APR - 4 1989

DIVISION OF GASTROINTESTINAL AND COAGULATION DRUG PRODUCTS

MEDICAL OFFICER's REVIEW OF THE FINAL REPORT ON THE ASPIRIN COMPONENT OF THE ONGOING PHYSICIANS' HEALTH STUDY

IND: 17-275
SPONSOR: Hennekens

This study was designed to test two primary prevention hypotheses:

1. Whether low-dose aspirin (325 mg) every other day reduces mortality from cardiovascular disease, and

2. Whether beta-carotene (50 mg) on alternate days decreases the incidence of cancer.

SUBJECTS: All male physicians 40-84 years old, residing in the U.S. at the beginning of the study (1982) were invited to participate. Invitations and questionnares were sent to 261,248 physicians. Of these 112,528 responded and 59,285 stated that they were willing to participate.

EXCLUSIONS: Subjects were excluded if they had a personal history of MI, stroke, TIA, cancer, current liver or renal disease, peptic ulcer, gout, contraindications to aspirin, or if they were using currently aspirin or other platelet active drugs or vitamin A supplements.

ELIGIBLE: Of the 59,285 physicians who responded, 33,223 were found to be eligible to enter the study. However, in order to exclude subjects unwilling or unable to comply with the study regimen the investigators carried out first an 18-week pilot study. This study eliminated about 1/3 of the responders. The number of eligible subjects which were actually enrolled in the study was 22,071.

The participants were randomized by a 2 x 2 factorial design into 4 study groups:

Active aspirin, active beta carotene:
Active aspirin,beta carotene placebo
Aspirin placebo, active carotene
Aspirin placebo, beta carotene placebo

Thus a total of 11,037 physicians were assigned to receive active aspirin and 11,034 to receive aspirin placebo.

Every 6 months for the first year and annually thereafter the participants were sent a supply of monthly calendar packs of:

White tablets containing aspirin or aspirin placebo for odd numbered days
and
Red capsules containing beta carotene or carotene placebo for even numbered days

They were also sent brief questionaires about compliance and relevant outcomes (MI, ischemic heart disease, sudden death, other cardiovascular death, stroke, or death from any cause).

On Dec 18, 1987 the Data Monitoring Board recommended early termination of the blinded aspirin component of the trial based on "the totality of evidence including 3 major considerations":

1. the presence of a statistically significant ($p<0.00001$) reduction in risk of total myocardial infarction among those in the aspirin group;

2. the inability of the trial to detect any effect of aspirin on cardiovascular mortality until the year 2000 or later due to the exceptionally low cardiovascular death rate of the participating physicians; and

3. the fact that over 85% of the participants experiencing non-fatal vascular events were subsequently prescribed aspirin, which made any finding concerning cardiovascular mortality particularly difficult to interpret.

The final report of the study presents the results of the cardiovascular component of the study as of January 25, 1988, the date participants were unblinded regarding their aspirin assignment. By that date the participants had a follow-up ranging from 45.8 to 77.0 months (average 60.2) with 99.7% of them still providing information about morbidity and compliance.

COMPLIANCE: 87.6% of the physicians reported that they took at least one type of pills and 83.0% that they took both types of pills as recommended. All subjects (100%) were followed up. There were no follow-up losses.

All diagnoses were confirmed by the End Points Committee (two internists, one cardiologist, and one neurologist), with all members blinded to treatment assignment. The diagnoses were based on the World Health Organization criteria and were documended by death certificates, hospital records and observer's impressions for deaths outside hospitals. All available information was collected. When written consent or the relevant records were not obtainable, a reported event was not considered confirmed. Records were available for review for 95.6% of the reported MIs, 95.2% of strokes and 94.8% of all deaths. All analyses were based on confirmed events.

Nonfatal Stroke was defined as a typical neurologic deficit, sudden or rapid in onset, lasting more than 24 hours and attributable to a cerebrovascular event. Nonfatal strokes were classified according to severity to mild (impairment not affecting functioning), moderate (functional impairement), and severe (a major change in lifestyle or dependency). Strokes were further classified according to etiology as ischemic or hemorrhagic.

The data were analysed by using life table statistics. For the end points of total myocardial infarction and total stroke, only the first event for a subject within that category was counted. If, however, a subject had two different events, a stroke and an MI, both events were counted. Fifteen subjects had both a nonfatal MI and a nonfatal stroke, i.e. each of these subjects provided two events. Twenty-three other subjects had a nonfatal MI or nonfatal stroke followed by cardiovascular death. For these subjects both, the fatal and nonfatal event were included in the analyses. Finally for the combined end point of nonfatal MI, nonfatal stroke and cardiovascular death, only a participant's first event was counted.

No participant was lost to follow-up. The reported consumption of aspirin was 85.71% in the aspirin group and 14.26% in the control group. Of the participants 624 taking aspirin and 645 taking placebo requested enteric coated preparations and an additional 16 assigned to aspirin and 13 assigned to placebo specifically requested Ecotrin or its placebo.

RESULTS

The investigators claim that the two groups were comparable regarding the baseline characteristics of age, smoking, diabetes mellitus, family history of MI, cholesterol levels, blood pressure, alcohol use, vigorous exercise and body mass index. However, a table showing the comparison of these characteristics has not been submitted. Although it can be seen from Table 4 "Risk of total myocardial infarction associated with aspirin use, by level of coronary risk factors" that the groups were balanced regarding these risk factors it is not known whether the values given represent baseline values or values obtained during the study when the reported events occurred.

The investigators found that there were 139 MIs among the physicians who were assigned to aspirin and 239 among those who were assigned to placebo (Table 1). Thus the relative risk for the aspirin subjects was reduced to 0.56 compared to the control subjects, and represents a very significant reduction ($p < 0.00001$). Ten of the aspirin MIs were fatal compared to 26 of the placebo MIs which were also fatal ($p < 0.007$).

The number of strokes which were experienced by the participants were also different but the results favored the placebo: the aspirin group had suffered 119 strokes, 9 of which were fatal, while the placebo group had suffered 98 strokes, 6 of which were fatal. These differences, however, were not found to be significant (p=0.15 and 0.43 respectively).

Ninety one (91) of the aspirin strokes and 82 of the placebo strokes (p=0.49) were found to be ischemic (Table 2), while 23 of the former and 12 of the latter were hemorrhagic (p=0.06). Thirteen of the aspirin and 6 of the placebo strokes were "moderate, severe, or fatal" (p=0.11). These results suggest that the risk for stroke in the aspirin group was increased by 2.14, while the risk of severe and fatal stroke was increased to 2.17. (these stastistics should be checked by our statisticians).

There were a total of 217 deaths in the aspirin group and a total of 227 deaths in the placebo group (p=0.64; Table 3). Twenty-three (23) of these deaths (12 in the aspirin and 11 in the placebo group) could not be confirmed due to unavailability of records. The confirmed deaths summarized from Table 3 were distributed as follows:

	ASPIRIN	PLACEBO	P value
AMI	10	28(26)*	0.004
Other Ischemic Heart Disease	24	25	
Sudden Death	22	12	0.09
Stroke	10(9)	7(6)	0.47
Other Cardiovascular deaths	15	11	0.43
Total Confirmed Cardiovascular Deaths:	81(80)	83(80)	0.87
Total Non Cardiovascular Deaths:	124	133	0.59
Total Confirmed Deaths:	205(204)	216(213)	0.60

* Numbers in parentheses indicate the number of deaths reported In Table 1 and the resulting new totals.

These results show that not only stroke but also sudden death and death from other cardiovascular causes were more frequent in the aspirin group and the total number of cardiovascular deaths was exactly the same in both groups (80 vs 80). The number of fatal MIs in the placebo group were reported in Table 1 to have been 26 not 28. The same table (Table 1) also shows that the number of deaths from stroke were 9 in the aspirin and 6 in the placebo group.

In order "to clarify a risk-to-benefit ratio" the investigators calculated a combined end point consisting of nonfatal MI, nonfatal stroke and cardiovascular death. Using this combined parameter they found that there were 307 important vascular events in the aspirin group and 370 in the placebo group ($p < 0.01$) They considered these results as suggesting an 18% reduction in "all important vascular events". However, as mentioned earlier, for these calculations the investigators counted only the first event for each subject. If a person had all 3 or any two of these events or if he had suffered multiple occurrences of any of these events, only his first event was counted. I do not believe that this is a fair representation of the quality of life of these individuals. I think for such an endpoint, and I would say for all end points, all events should be counted not only first events. Repeat MIs and repeat strokes can be just as painful and incapacitating as first MIs or first strokes.

The investigators also examined the effect of aspirin among subgroups of physicians with various risk factors (Table 4). They found that aspirin reduced the risk of MI in patients aged 50 years and over (p 0.02), but they found no relationship between age and the effect of aspirin on stroke or cardiovascular mortality in genaral. However, no data for this lack of relationships are shown.

The investigators further claim that aspirin reduced the incidence of MI in all subjects regardless of cholesterol levels, and that the effect was greater in those with the lowest cholesterol levels (209 mg/100ml; p=0.04).

Regarding cigarette smoking the study showed that aspirin reduced the incidence of MI in all subgroups - smokers, nonsmokers or former smokers. However the differences from placebo were not significant. The investigators further claim that "For cardiovascular mortality, there appeared to be effect modification by cigarette smoking (p=0.05). However, neither the observed reduction among nonsmokers (p=0.18) nor the apparent increased risk among current smokers (p=0.20) was statistically significant". No results for this claim are shown.

Finally, the investigators found that aspirin did not significantly modify the effect of blood pressure, alcohol consumption, vigorous excercise or body mass index on the incidence of MI, stroke, or cardiovascular mortality (data shown only for MI).

Side Effects: The reported effects were mainly gastrointestinal and are tabulated in Table 5. No significant differences between the two groups were reported except regarding the incidence of duodenal ulcers, bleeding and general non-infectious disorders of the GI tract (p=0.04). The investigators claim that ulcers were observed in 166 aspirin and in 138 placebo participants (p=0.11). However, addition of the pertinent values from Table 5 (12 + 26 + 54 + 157 + 4 for aspirin and 6 + 16 + 29 + 133 + 4 for placebo) gives a total of 253 ulcers for the aspirin and 188 ulcers for the placebo group. Also, the numbers for "Gastrointestinal symptoms (except ulcer)" and the total numbers for bleeding problems were all wrong. I calculated these values and I came up with quite different numbers than those reported in Table 5. My numbers are as follows:

	Aspirin	Placebo
Gastrointestinal symptoms (except ulcer)	6261 (56.7%)	6134 (55.6%)
Bleeding Problems	3999 (36.2%)	2942 (26.7%)

In other words the total incidence of side effects was much higher for both groups than it was reported by the authors.

Thirty seven (37) of the aspirin and 22 of the placebo ulcers bled (p=0.05). The aspirin physicians experienced significantly more easy bruising ($p < 0.0001$), melena ($p < 0.00001$), epistaxis ($p < 0.0001$) or "other bleeding" ($p < 0.0003$) than the placebo physicians. Forty-eight (48) of the aspirin and 27 of the placebo physicians required transfusions (p=0.02) and [illegible] died from G.I. hemorrhage.

DEFICIENCIES:

1. The study was inherently least suitable to show significant differences within a reasonable period of time. The participants by study design were more or less at low risk for cardiovascular events. Subjects with a personal history of MI, stroke, or TIA were excluded from participating. In addition, as physicians, these subjects knew better than the general public how to protect themselves from cardiovascular events. They had more or less controlled their risk factors. If the risk factors used in Table 4 represent baseline values, these values show that only 11% of the aspirin participants and 10% of the placebo participants had diastolic blood pressures equal or above 90 mm Hg (see Table A which I made using the values in Table 4); and only 11% in each group were current smokers; 75% of the participants (in both groups) were below 60 years of age, the age when clinical cardiovascular events normally begin; 87% and 86% had no parental history of cardiovascular disease; and 73% and 72% were exercising regularly. The only risk factors of some significance were the blood cholesterol levels and body weight: about one half of the participants in both groups had cholesterol levels over 210 mg/100 ml and about 35% were overweight; 25% of all subjects were obese.

2. The investigators discussed the effect of aspirin on the risk factors regarding stroke and cardiovascular mortality without submitting any data. Specifically, they failed to present the data regarding the effect of aspirin on cardiovascular mortality in smokers or nonsmokers, although they claim that "there appeared to be effect modification by cigarette smoking ($p=0.05$)".

3. It is stated that 14% of the placebo patients were prescribed aspirin after they had a nonfatal cardiovascular event. If these patients had subsequently a secondary cardiovascular event which was different from the original event or if they died how was the secondary event counted? With the placebo or with the aspirin events?

4. Case report forms of the patients with end-points have not been submitted. The fact that diagnosis of end points was confirmed by an End Points Committee does not necessarily mean that FDA must accept the data at their face value without checking the CRFs. How sudden deaths were differentiated from AMIs? One has to be reminded of the anturane study to realize how unreliable this assumption can be. Besides, it would be unfair to the Pharmaceutical Industry if we accept other sponsors' claims without verification. The mathematical discrepancies in Tables 1, 3 and 5, which I mentioned before indicate that the investigators were not careful with their data or that they changed some results in the process of writing this paper. Either way, at least some of the data, are suspect.

Even if we accept the data at their face value, this study does not provide evidence that ingestion of 325 mg of aspirin every other day is beneficial i.e. that the benefits outweigh the risks. The great reduction in the incidence of MI which is being claimed that aspirin induced, was counter-balanced by a greater incidence in strokes, especially severe, fatal,

hemorrhagic strokes, and also by a greater incidence in sudden death and "other" cardiovascular deaths. The reason that the differences in the last 3 categories of death did not reach statistical significance in favor of placebo is due to the fact that these differences were split among 3 categories, while the favorable aspirin effect was concentrated all in the MI. The total number of cardiovascular deaths in the aspirin and the placebo group was exactly the same (80 vs 80). Furthermore, we should consider the fact that it is generally more incapacitating to survive a stroke than to survive a heart attack. The investigators have not identified any group in which aspirin could reduce the incidence of heart attacks without increasing the incidence of stroke, sudden death or of other cardiovascular death.

We should also not forget that aspirin increased the incidence of bleeding and the need for transfusions significantly. One subject actually died from G.I. bleeding. These events happened in a group of people who were selected regarding their sensitivity to aspirin. Subjects which were unable to tolerate this drug were excluded during the prerandomization pilot study.

RECOMMENDATION: Considering that at their face value the results of this study do not show that the claimed benefits in the incidence of MI outweigh the risks of an increased incidence in strokes, sudden death and other cardiovascular deaths, I do not believe that FDA should consider the possibility of approving aspirin for prophylaxis from primary MIs. Consequently, review of the CRFs of the patients with end point events will serve no practical purpose. Scientifically, it may be interesting to go through those records and see whether the published results are really supported by the actual data or whether other significant relationships can be found.

Do we have the time and the authority for this, if the sponsor does not want to request approval for a new indication?

If FDA decides to publish a critique of the study after its publication, a statistician should review the statistics.

E. Triantas, MD
E. Triantas, M.D.

ATTACHMENTS:
Tables 1-5, and A

cc:
IND-17,275
HFD-180
HFD-180/CSO
HFD-180/SFredd
HFD-180/ETriantas
ft/jgw/4/3/89/w0004T

4/4/89
I do not agree with this negative assessment. A 47% reduction in fatal MI is an important effect. Nevertheless, the trend to increased cerebral hemorrhage (also suggested by the British Heart Study) and the non-replication of the results in that study (which may be explainable) give me pause as to whether the drug should be labeled for this benefit. I will need full information for review as per this letter of July 5, 1988.
M.D.

Table 1. Confirmed* Cardiovascular End Points in the Aspirin Arm of the Physicians' Health Study, According to Treatment Group

END POINT	ASPIRIN	PLACEBO	RELATIVE RISK	95% CONFIDENCE INTERVAL	P-VALUE
Myocardial infarction					
Fatal	10	26	0.34	0.15-0.75	0.007
Nonfatal	129	213	0.59	0.47-0.74	<0.00001
Total	139	239	0.56	0.45-0.70	<0.00001
(person-years)	(54555.0)	(54360.7)			
Stroke					
Fatal	9	6	1.51	0.54-4.28	0.43
Nonfatal	110	92	1.20	0.91-1.59	0.20
Total	119	98	1.22	0.93-1.60	0.15
(person-years)	(54645.3)	(54640.8)			

*Additional events that could not be confirmed due to unavailability of records included 17 myocardial infarctions (10 in aspirin and 7 in placebo) and 11 strokes (3 in aspirin and 8 in placebo).

Table 2. Subgroups of Strokes Classified as Ischemic or Hemorrhagic, According to Severity*

END POINT	ASPIRIN	PLACEBO	RELATIVE RISK	95% CONFIDENCE INTERVAL	P-VALUE
Ischemic etiology					
Mild	69	61	1.13	0.80-1.60	0.48
Moderate, severe, or fatal	21	20	1.05	0.57-1.95	0.88
Unknown severity	1	1			
Total	91	82	1.11	0.82-1.50	0.49
Hemorrhagic etiology					
Mild	10	6	1.67	0.61-4.57	0.32
Moderate, severe, or fatal	13	6	2.19	0.84-5.69	0.11
Total	23	12	2.14	0.96-4.77	0.06
Unknown etiology					
Mild	2	1			
Moderate, severe, or fatal	1	2			
Unknown severity	2	1			
Total	5	4			
Total	119	98	1.22	0.93-1.60	0.15

* Severity was defined as follows: mild, impairment not affecting functioning; moderate, functional impairment; and severe, a major change in life style or dependency.

Table 3. Confirmed Deaths According to Treatment Group

CATEGORY OF DEATHS (9th ICD CODES)	ASPIRIN	PLACEBO	RELATIVE RISK	95% CONFIDENCE INTERVAL	P-VALUE
Total cardiovascular deaths†	81	83	0.96	0.60-1.54	0.87
Acute myocardial infarction (410)	10	28	0.31	0.14-0.68	0.004
Other ischemic heart disease (411-414)	24	25	0.97	0.60-1.55	0.89
Sudden death (798)	22	12	1.96	0.91-4.22	0.09
Stroke (430,431, 434,436)‡	10	7	1.44	0.54-3.88	0.47
Other cardiovascular (402,421, 424,425,428,429, 437,440,441)	15	11	1.38	0.62-3.05	0.43
Total noncardiovascular deaths	124§	133	0.93	0.72-1.20	0.59
Total deaths with confirmed cause	205	216	0.95	0.79-1.15	0.60
Total deaths¶	217	227	0.96	0.80-1.14	0.64
(person-years)	(54889.5)	(54869.2)			

† For this analysis, all fatal cardiovascular events are included, regardless of prior nonfatal event.

‡ This includes ischemic: 3 aspirin, 3 placebo; hemorrhagic: 7 aspirin, 2 placebo; unknown etiology: 0 aspirin, 2 placebo.

§ This includes the one death due to gastrointestinal hemorrhage

¶ Additional events that could not be confirmed due to unavailability of records included 23 deaths (12 in aspirin and 11 in placebo), of which 11 were suspected to be cardiovascular (7 in aspirin and 4 in placebo) and 12 noncardiovascular (5 in aspirin and 7 in placebo).

Table 4. Risk of Total Myocardial Infarction Associated with Aspirin Use, by Level of Coronary Risk Factors

	ASPIRIN		PLACEBO			P-VALUE (Trend in RR)
	MI/Total	%	MI/Total	%	RR	
Age (years)						
40-49	27/ 4526	0.6	24/ 4525	0.5	1.13	
50-59	51/ 3725	1.4	87/ 3725	2.3	0.58	
60-69	39/ 2045	1.9	84/ 2045	4.1	0.46	
70-84	22/ 740	3.0	44/ 740	6.0	0.49	0.02
Smoke Cigarettes						
Never	55/ 5431	1.0	96/ 5488	1.8	0.58	
Past	63/ 4372	1.4	105/ 4302	2.4	0.59	
Current	21/ 1213	1.7	37/ 1225	3.0	0.57	0.99
Diabetes Mellitus						
Yes	11/ 275	4.0	26/ 258	10.1	0.39	
No	128/10749	1.2	213/10764	2.0	0.60	0.22
Parental History of MI						
Yes	23/ 1420	1.6	39/ 1432	2.7	0.59	
No	112/ 9505	1.2	192/ 9481	2.0	0.58	0.97
Cholesterol level (mg/100 ml)						
$\leq$ 159	2/ 382	0.5	9/ 406	2.2	0.23	
160-209	12/ 1587	0.8	37/ 1511	2.5	0.29	
210-259	26/ 1435	1.8	43/ 1444	3.0	0.61	
$\geq$ 260	14/ 582	2.4	23/ 570	4.0	0.59	0.04
Diastolic blood pressure (mm Hg)						
$\leq$ 69	2/ 583	0.3	9/ 562	1.6	0.21	
70-79	24/ 2999	0.8	40/ 3076	1.3	0.61	
80-89	71/ 5060	1.4	128/ 5084	2.5	0.55	
$\geq$ 90	26/ 1037	2.5	43/ 970	4.4	0.56	0.88
Systolic blood pressure (mm Hg)						
$\leq$ 109	1/ 330	0.3	4/ 296	1.4	0.22	
110-129	40/ 5071	0.8	75/ 5130	1.5	0.52	
130-149	63/ 3829	1.7	115/ 3861	3.0	0.55	
$\geq$ 150	19/ 454	4.2	26/ 412	6.3	0.65	0.48

Table 4 (continued)

	ASPIRIN		PLACEBO			P-VALUE (Trend in RR)
	MI/Total	%	MI/Total	%	RR	
Alcohol use						
Daily	26/ 2718	1.0	55/ 2727	2.0	0.45	
Weekly	70/ 5418	1.3	112/ 5314	2.1	0.61	
Rarely	40/ 2802	1.4	65/ 2897	2.2	0.63	0.26
Vigorous exercise at least once/week						
Yes	91/ 7909	1.2	140/ 7862	1.8	0.65	
No	45/ 2997	1.5	92/ 3060	3.0	0.49	0.21
Body mass index (kg/m^2)						
$\leq$ 23.0126	26/ 2871	0.9	41/ 2805	1.5	0.62	
23.0127-24.4075	32/ 2700	1.2	46/ 2627	1.8	0.68	
24.4076-26.3865	32/ 2713	1.2	75/ 2823	2.7	0.44	
$\geq$ 26.3866	49/ 2750	1.8	76/ 2776	2.7	0.65	0.90

Table 5. Side Effects by Treatment Group

CATEGORY OF EVENTS (9th ICD CODES)	ASPIRIN N	ASPIRIN %	PLACEBO N	PLACEBO %	P-VALUE
Gastrointestinal symptoms (except ulcer)	3833	34.7	3772	34.2	0.49
GI discomfort (535)	2897	26.2	2844	25.8	0.49
Other non-infectious disorders of the digestive tract (536,537.8,537.9)	391	3.5	336	3.0	0.04
Miscellaneous symptoms of the digestive tract (533.123,787,789.0)	2973	26.9	2954	26.8	0.82
Upper GI ulcers	166	1.5	138	1.3	0.11
Esophageal ulcer (530.2)	12	0.1	6	0.05	0.16
Gastric ulcer (531)	26	0.2	16	0.1	0.12
Duodenal ulcer (532)	54	0.5	29	0.3	0.006
Peptic ulcer (533)	157	1.4	133	1.2	0.16
Gastrojejunal (534)	4	0.04	4	0.04	0.99
Bleeding problems	2967	26.9	2235	20.3	<0.0001
Easy bruising (459)	1579	14.3	1021	9.3	<0.0001
Hematemesis (578.0)	37	0.3	28	0.2	0.26
Melena (578.1)	358	3.2	243	2.2	<0.00001
Nonspecific GI bleeding (578.9)	433	3.9	412	3.7	0.47
Epistaxis (784.7)	859	7.8	639	5.8	<0.0001
Other bleeding* (599.7,958.2)	733	6.6	599	5.4	0.0003

*29% were related to shaving or brushing teeth (31% aspirin, 26% placebo), and 71% were hematuria (69% aspirin, 74% placebo)

TABLE A

BASELINE CHARACTERISTICS
(Calculated from Table 4)

	Aspirin	Placebo
Age (years)		
40-49	41%	41%
50-59	34%	36%
60-69	19%	19%
70-84	7%	7%
Cigarette Smoking		
Never	49.3%	49.83%
Past	40%	39%
Current	11%	11%
Parental History of MI		
yes	13%	13%
No	87%	86%
Cholesterol Levels (mg/100ml)		
<159	10%	10%
160-209	40%	38%
210-259	36%	37%
>260	15%	15%
Diastolic Blood Pressure (mm Hg)		
< 69	6%	6%
70-79	31%	32%
80-89	52%	52%
> 90	11%	11%
Vigorous Exercise at least once/week		
Yes	73%	72%
No	27%	28%
Body Mass Index Kg/H^2		
< 23.01	26%	25%
23.01-24.40	24%	24%
24.41-26.39	25%	26%
> 26.39	25%	26%

Body Mass Index of 25-27.8 in males indicates overweight, > 27.8 indicates obesity.

OCT 31 1989

DIVISION OF GASTROINTESTINAL AND COAGULATION DRUG PRODUCTS

MEDICAL OFFICER'S REVIEW

IND: 17-275

DRUG: Aspirin

SPONSOR: Charles Hennekens, M.D.
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DATE OF SUBMISSION: September 28, 1989

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This submission contains:

1. The response of the PHS Research Group to our Medical and Statistical reviews of their Aspirin Study,

2. A reprint of this study: the "Final Report on the Aspirin Component of the Ongoing Physicians' Health Study",

3. A copy of the Galley Proofs of the review article " Aspirin and Other Antiplatelet Agents in the Secondary and Primary Prevention of Cardiovascular Disease",

4. A reprint of the review article "Guide to Clinical Preventive Services", and

5. A manuscript entitled "The effect of Aspirin on Clinical Characteristics of Nonfatal MI in a Randomized Trial of Physicians"

Item 1. Response of the PHS Research Group to the FDA Medical Review.

This response was written by Dr. James O. Taylor, the Chairman of the Endpoints Committee.

The parts of the Response which need to be addressed here are:

a) Choice of Diagnostic criteria

It appears that there is a misunderstanding. The members of the Endpoints Committee think that:

1. I (the Medical Reviewer) felt that the Endpoints Committee did not consistently apply the endpoint definitions and criteria which were stated a priori.

2. I had basic disagreement with the criteria as stated.

These comments refer to the MI diagnostic criteria. I have no disagreement with these criteria or their application. My disagreement with the Endpoints Committee refers to whether they are justified to classify patients in the sudden death category as though they were sure that the death of these patients was due to a cause different from acute MI.

The PH Study was not a routine drug efficacy study. The patients were not treated in a hospital facility nor were they followed regularly by a physician-investigator. The participants were followed by correspondence only. When a death occurred the investigators were not notified immediately. They were only informed post-hoc with the return of the annual Questionnaires. Then, if the proper tests or an autopsy had not been performed, it was not possible for them to make sure whether the death was due to an acute MI or not. All these measures were left to the discretion of the participant's physician. In other words, in such cases the particular patients who were classified in the sudden death category in the PHS study did not meet the specific criteria of an acute MI not because they were tested and failed to meet these criteria but simply because they were not examined and/or tested properly at the time of the event. By classifying the cases which were fully studied in the "MI" category and all the cases, which were incompletely investigated or were not investigated at all, in the "Sudden Death" category, the investigators give a false impression of the effectiveness of the drug. Due to the nature of their study, their data do not allow them to separate these categories.

b) Exclusion of Patients with Preexisting MIs:

Dr Taylor makes the statement that "applying an additional screening test to eliminate possible preexisting MIs in what was clearly a low prevalence population would have primarily resulted in the elimination of people with preexisting MI and would have a very negative effect on the trial's power to detect a significant effect of aspirin."

This very statement indicates that the investigators themselves believe that most of the effect of aspirin in the Physicians' Health Study was due to the prevention of secondary MIs. Plain reduction in the number of patients would not reduce significantly the power of the study to detect a significant difference between aspirin and placebo. Even, if the total number of patients is reduced to 5000 (from 22000), the number of expected nonfatal MIs would be 129x5/22=29 cases for the aspirin group and 213x5/22=48 cases for the placebo group, a 40% difference, which is more than enough to show whether aspirin prevents primary MIs or not, if indeed the difference which was detected in the Physicians' Health Study was due to the prevention of primary MIs.

c) Case by Case Comments of Dr. Taylor:

Nonfatal MIs:

I had not disputed cases: 1538887
2721522
3702270
2202155

Case 1729580 (not included in the analysis): Explanation accepted.

Patients # 3793404 and 4222034 (both placebo): My notes show "disconfirmed" for both cases. I must have made a mistake, although it is hard to understand it.

Deaths from MI:

I had disputed only cases:

3151302 (placebo). I had not seen the autopsy report.

1841300 (placebo). As Dr. Taylor says this patient died from massive stroke two months after his CABG. He did not die from complications of the surgery. His death should have not been classified among the MI group deaths but among the stroke deaths.

I had not disputed any of the other cases mentioned in Dr. Taylor's report. It is, however, informative that he described the cases.

Sudden Deaths:

Case 3129252: It appears that an autopsy was not done. I was mistaken.

Case 2652327 (aspirin): This patient had severe pain and vomited. Vomit is one of the atypical MI symptoms. The patient had severe coronary atherosclerosis. The possibility that he had died because of an acute MI cannot be excluded.

Cases: 3333659 (aspirin) and 3900939 (placebo): The sentence: "The only indications for the occurrence of MIs in these cases were found microscopically" is unfortunate. I wanted to say that the only indications for the formation of an infarct in these cases were found microscopically. My intention in mentioning these cases was to stress the fact that a visually

obvious infarct needs time to develop after an AMI occurs. If the patient dies quickly within 1 or 2 hours the autopsy does not show any grossly visible infarct. The only evidence in such cases can be found by a microscopical examination. I chose cases 3333659 and 3900939 because they were confirmed MIs and the patients had died fast.

I had no disagreement with the symptomatology of the remaining patients

d) Regarding Tables 11 and 12 of my review of September 1, 1989 (second part of review of the June 9, 1989 submission) I would like to add that:

a) The listing of the patients who had "old" MIs or were subjected to CABG and/or PTCA is not complete as I stressed in my review.

b) The total number of patients in each group was different. There were 287 patients in the placebo group and 204 in the aspirin group. Although, the total number of patients who had "old" MIs and/or corrective procedures was the same in the 2 groups, the incidence was different: 4.5% of the placebo patients had old MIs vs 6.4% of the aspirin patients and 5.2% of the former had corrective procedures compared to 7.8% of the latter (see new Tables 11 and 12). In both cases the incidence was higher in the aspirin cases, which suggests that the finding that the aspirin patients had significantly fewer MIs may be spurious. I tried to point out this fact at the Advisory Committee Meeting but I do not think that I came across.

Items 2-4 have been submitted before and have already been reviewed (MOR of July 10, 1989).

Item 5: In this manuscript the PHS Research group compare the clinical characteristics and the angiographic findings of the patients who suffered nonfatal MIs in the Physicians' Health Study. They found "no significant difference in the size, location, electrocardiographic features or clinical severity of infarction between the aspirin and placebo groups" and "no differences in the distribution or number of coronary vessels obstructed based on treatment assignment". They concluded that "...platelet inhibition for up to 60.2 months does not significantly alter the progression of atherosclerosis"

RECOMMENDATIONS: Before any changes in the aspirin insert are implemented FDA should request that the investigators go back in their files, find all patients who had:

a) Evidence of old MIs,

b) CABG or PTCA,

c) Taken regularly cardiovascular medication (B-blockers, Ca channel blockers, etc.),

and compare the groups regarding these parameters.

E. Triantas, MD
E. Triantas, M.D.

cc:
IND-17,275
HFD-180
HFD-180/CSO
HFD-180/SFredd
HFD-180/JChoudary
HFD-180/JGibbs
HFD-180/ETriantas
ft/jgw/10/12/89/w0016T

10/31/89
Noted. Requested data on cardiovascular meds. Response from Dr. Hennekens indicates that at baseline very few patients were taking B-blockers etc. (by questionnaire), and since randomization info on the use of these meds was not systematically collected. Evidence of old MI's, PTCA's or CABGs will not likely change finding of reduction in odds ratio of treated patients. Will discuss in transmittal memorandum.

SF

STATISTICAL REVIEW AND EVALUATION

SEP 11 1989

IND No.: 17,275
Subject: Aspirin Mortality Prevention Trial
Document Reviewed: Study report consisting of Attachments I - X, dated June 9, 1989.

This review was completed after discussion with Dr. Triantas, the medical reviewer, and Dr. Stephen Fredd, Director of Gastrointestinal Division.

This review pertains to the U.S. Physician's Health Study (PHS). This study is a randomized, double-blinded, placebo-controlled clinical trial of aspirin in the prevention of cardiovascular disease and of beta-carotene in the prevention of cancer. The blinded aspirin component of the trial was terminated earlier than planned, while the beta-carotene component is still ongoing.

1. Study Protocol

1.1 Study Objectives

Two primary prevention hypotheses of concern in the PHS study are: (1) whether the low-dose aspirin (325 mg taken every other day) reduces mortality from cardiovascular disease, (2) whether the beta-carotene (50 mg on alternate days) decreases the incidence of cancer, in healthy human subjects who have not previously had a myocardial infarction, stroke, transient cerebral ischemia or cancer (except non-melanoma skin cancer).

Secondary objectives are the effect of aspirin on the onset rates of certain non-fatal cardiovascular diseases (particularly, MI and stroke) and the effect of beta-carotene on the onset rates of various epithelial cancers and non-melanoma skin neoplasms. It was also hoped that this large trial would provide conclusive evidence as to the side effects of the low-dose aspirin and the low-dose beta-carotene.

Primary endpoints are total mortality, total cardiovascular mortality, and total cancer incidence. Secondary endpoints include the incidences of MI, stroke and transient ischemic attack, and angina pectoris. Criteria for defining these endpoints are provided on pages 5.11-5.17 of Attachment X.

1.2 Study Design

The study subjects were male US physicians, aged 40 to 84 years at entry. Originally, those 40-49 years of age were not to be included. The inclusion of these younger subjects was based on pilot studies indicating that slightly fewer than anticipated physicians would be willing and eligible to participate.

Prior to randomization, there was an 18 weeks run-in period in which all potential participants were taking study pills. This run-in was designed to eliminate most of the poor compliers, those unable to tolerate study pills and those who would drop out or would not have returned their forms when asked to do so.

All physicians who were still willing and eligible and who had taken their pills at least 65% of the time were randomized to one of the following groups: (1) those taking one 325 mg aspirin tablet every other day, alternating with one 50 mg capsule of beta-carotene; (2) those taking one aspirin tablet every other day, alternating with one capsule of beta-carotene placebo; (3) those taking one aspirin placebo tablet every other day, alternating with one beta-carotene capsule; (4) those taking one aspirin placebo tablet every other day, alternating with one capsule of beta-carotene placebo. Bristol-Myers provided the aspirin (Bufferin) and BASF provided beta-carotene (Lurotin). Treatment allocation was made within each of the following age groups: 40-44, 45-49, 50-54, 55-59, 60-64, 65-69, 70-75, 76-79, and 80-84.

To maintain the uniform applicability of eligibility criteria, ineligible subjects who were not identified during the run-in period were excluded even after they were randomized. Post-randomization exclusions were to be blinded to treatment assignment and to be based on uniformly collected clearcut evidence that ineligibility had occurred between the run-in questionaire and the date of randomization.

1.3 Statistical Methods

Log rank method was used to analyze event rate, number of events per person-year, where person years were computed from date of randomization to date of event or death or date of analysis based on all subjects randomized. Regarding the effect of aspirin, a comparison in cardiovascular death rates among those who were assigned to aspirin and those who were assigned to aspirin placebo was made separately in the beta-carotene group and in the beta-carotene placebo group. Then these two differences were combined to test whether, in aggregate, aspirin is of any real benefit.

In estimating a relative risk (or odds ratio), the ratio of the observed event rate in the aspirin group divided by that in the placebo group was calculated for each stratum. The relative risk was then estimated by a weighted average of these stratum-specific ratios, with weights equal to the inverse variance derived from a Taylor Expansion.

If other cardiovascular risk factors differed between the treatment groups, adjustment was made using Cox's regression analysis or the log rank method with retrospective stratification (based on these factors).

In calculating sample size, the cardiovascular mortality rate in the placebo group was assumed to be about 5% in four and a half years. Over 20,000 physicians were needed to detect a 20% reduction (i.e., an absolute reduction of 1%) in cardiovascular mortality in the aspirin takers with a power of at least 92% and a 5% significance level. It was later proposed to extend the original follow-up period of 4½ years to 7½ years, due to lower than anticipated endpoint rates.

It was planned that data would be examined annually. The trial would continue to the end unless the chi-square test comparing treatments would reach an extreme value such as 9.0 at an interim look. If the trial did not stop prior to the end, ordinary statistical analysis would be undertaken.

2. Study results

A total of 22,071 out of 33,223 physicians enrolled in the run-in were randomized. The early termination of the aspirin component of the trial was recommended on December 18, 1987, due (according to attachment II of their report) to three primary considerations: (1) the presence of a statistically significant ($p<0.00001$) reduction in risk of total MI in the aspirin group; (2) the inability of the trial to detect any effect of aspirin on cardiovascular mortality until the year 2000 or later (due to the exceptionally low cardiovascular death rates of participating physicians); and (3) the fact that over 85% of participants experiencing nonfatal vascular events were subsequently prescribed aspirin. The final analyses of the cardiovascular component up to January 25, 1988 were reported. All analyses were based on confirmed cases.

2.1 Deaths

There were 81 cardiovascular deaths in the aspirin group and 83 in the placebo group (relative risk = 0.96, $p=0.87$). It was claimed that there was a statistically significant finding - a

reduction in fatal MI (10 in aspirin, 28 in placebo, p=0.004). There was an apparent but not statistically significant increase in sudden death (22 in aspirin, 12 in placebo, p=0.09). Summary is provided in Table 1.

2.2 Total MI

There were 139 total MI (fatal and nonfatal) in the aspirin group and 239 in the placebo group; the 44% reduction in the risk of having MI in the aspirin group was statistically significant (p<0.00001, Table 2).

2.3 Total Stroke

There were 119 cases of stroke in aspirin and 98 in placebo; this 22% increase in the risk of total stroke was not statistically significant (p=0.15, Table 2). An increase of 14% in the risk of hemorrhagic stroke was observed in the aspirin group (23 in aspirin vs. 12 in placebo, p=0.06, Table 3).

2.4 Baseline characteristics

There were no differences between the two treatment groups in the following baseline characteristics: age, cigarette smoking, diabetes mellitus, parental history of MI, cholesterol level, systolic blood pressure, diastolic blood pressure, alcohol use, vigorous exercise, and body mass index. The possible effects of any small differences in these risk factors were adjusted through logistic regression. The relative risk for each cardiovascular endpoint was not changed (Table 4, requested by these reviewers).

2.5 Endpoint combination

Combining fatal acute MI with all other fatal ischemic heart disease resulted in 34 deaths in aspirin and 53 in placebo (relative risk = 0.60, p=0.04). A combined endpoint consisting of nonfatal MI, nonfatal stroke and cardiovascular death was also considered. The relative risk in this endpoint is 0.82 (307 in aspirin and 370 in placebo, p=0.01). The PHS research group claimed that this represents a statistically significant 18% reduction in important vascular events among those assigned to aspirin.

2.6 Subgroup results

Possible effects of aspirin among subgroups of physicians with various cardiovascular risk factors were examined. It was reported that the reduction in the risk of MI associated with aspirin was apparent for those 50 years or older. This beneficial effect was apparent in all cholesterol strata but

unexpectedly was the greatest at lower levels of cholesterol. Details were presented in Table 5. The PHS group commented that this data-derived hypothesis might be real or might reflect random fluctuations in the data. For stroke and cardiovascular mortality, no consistent effects of aspirin were observed with the possible exception of cigarette smoking in relation only to cardiovascular mortality. The PHS group did state that any subgroup analysis of these endpoints (i.e., stroke and cardiovascular death) would be difficult to interpret since the numbers with these endpoints were too small even for detecting whether there were any meaningful overall results.

2.7 Side effects

There were 169 subjects with ulcer in the aspirin group compared to 138 in the placebo group (relative risk 1.22, p=0.08). Among these subjects, a 77% increase in risk of experiencing hemorrhage was observed in the aspirin group (38 in aspirin vs. 22 in placebo, p=0.04). The aspirin group reported greatly more incidences of bleeding such as easy bruising, hematemesis, melena, nongastrointestinal bleeding, epistaxis, or other bleeding (relative risk = 1.32, p<0.00001). Forty-eight physicians in the aspirin group and 28 in the placebo group required transfusion (p=0.02). The aspirin group reported one fatality from gastrointestinal hemorrhage. Details were provided in Table 6.

3. Reviewers' Evaluation and Comments

3.1 Total MI

The primary endpoints of the U.S. Physician's Health Study were total cardiovascular mortality and cancer incidence. The early stopping rule (originally laid out in the grant proposal but not in the protocol) states that the trial would continue unless chi-square test comparing treatments reaches an extreme value such as 9.0 (i.e., if p<0.0027, then the trial would be stopped). However, it was never stated which endpoint the early stopping rule was based on. The trial was terminated early for several reasons; two of them were the overwhelming evidence showing the beneficial effect of aspirin on MI and the inability of this trial to show an effect on total cardiovascular mortality within the proposed follow-up period. According to the study protocol, the incidence of MI was a secondary endpoint. If the stopping rule was based only on total cardiovascular mortality, then the trial would not have been terminated and hence it is not clear how to assess the statistical evidence regarding the benefit of aspirin on MI or total mortality or other endpoints. If the stopping rule was applied to every endpoint, then one encountered

the problem of how to adjust the reported p-values retrospectively since a proper way of adjusting was never mentioned in the protocol or the grant proposal. The Bonferroni-type adjustment, though usually extremely conservative, will be applied. Based on this type of adjustment for multiple endpoints, the reduction in the risk of MI in the aspirin group is still statistically significant. The differences in the risk of MI appears numerically in favor of aspirin in all strata of each cardiovascular risk factor recorded, except for those 40-49 years of age (Table 5).

Dr. Triantas had some disagreement with the PHS group's classification of some of the nonfatal MIs. She reported that there could be 210 cases of nonfatal MI in the placebo group versus 131 cases in the aspirin group ($p<0.0002$, based on our "crude" calculation using two-sample t-statistic). According to her counts for total MI, the conclusion regarding the reduction in the risk of total MI in the aspirin group remains unchanged (249 in placebo vs. 163 in aspirin, $p<0.00001$) based on our "crude" analysis.

From the results given above, aspirin 325 mg taken every other day seems to reduce the incidence of MI. However, from this finding, can one conclude that aspirin reduces the risk of having first MI? This question will be discussed next.

3.2 Prevention of first MI

According to the protocol, the subjects should not have had a myocardial infarction before randomization. However, from the records of some of the patients, Dr. Triantas found that roughly 8% of the 512 subjects who reported nonfatal MIs had evidence of an old MI. Time of occurrence of these old MIs could not be ascertained. More importantly, the exact number of such cases with prior MIs before randomization in the entire randomized population is not known. Therefore, it is not possible for us to assess whether the deletion of these cases that should have been excluded from the analysis will alter the result. In our view, it is premature to make the claim that aspirin reduces the risk of having first MI. The PHS group should reexamine their data and address this issue.

3.3 Fatal MI and combined endpoint

In our view, the reduction in the risk of fatal MI is not statistically significant based on the Bonferroni-type adjustment [comparing the claimed p-value of 0.004 against 0.0027/(number of endpoints)]; in fact, the statistical significance was not reached even without any adjustment for multiple endpoints ($p=0.004 > 0.0027$). In addition, according to Dr. Triantas, some

of the sudden deaths should have been classified as "possible MIs" and the cause of death of the remaining patients cannot be established with certainty due to a lack of adequate information. Based on her reclassification, there could have been 32 cases of fatal MI (verified MI plus possible MI) in the aspirin group versus 39 cases in the placebo group; this difference is not statistically significant ($p > 0.50$). Likewise, the 18% reduction in the incidence of the combined endpoint (Section 2.5) is not statistically significant (the reported $p=0.01 >> 0.0027$). Therefore, we feel that the trial has not yet produced conclusive evidence regarding the beneficial effects of aspirin on fatal MI or the so-called combined endpoints.

3.4 Strokes

The increase in the risk of nonfatal stroke in the aspirin group was shown numerically in those aged 50 years or above (Table 7). It was also consistently observed regardless of etiology or degree of severity (Table 3).

3.5 Blinding

Due to the length of this study and the fact that the studied medications were mailed to the participants every 6 months, it is not possible to carry out this study in a "standard" double-blinded manner. The protocol stated that Dr. Bernard Rosner, the co-investigator and chief statistician of the trial, is the sole individual who monitored the unblinded data. However, due to the nature of this trial, Charlene Belanger (PHS project coordinator) and Fran Stubblefield (Head of Data Processing Department of the PHS Research Group) also had access to the unblinded data. The unblinding will not bias the results if they do not, directly or indirectly, influence the outcome of the participants (e.g., confirmed major vascular events). However, such an assumption is probably difficult to check.

The investigators recognized that with the medical knowledge and resources of the participants, it would be relatively easy for these physicians to unblind themselves, perhaps unconsciously. The potential bias due to such unblinding, if any, is also difficult to evaluate.

The profile of side effects is left to the medical experts.

4. Summary

The U.S. Physician's Health Study did not establish evidence regarding total cardiovascular mortality which was one of the

primary endpoints.

The benefit of aspirin in reducing the incidence of MI seems apparent in the healthy male physicians aged 50-84 (a selected population). However, it is premature to conclude that aspirin can reduce the risk of first MI because of the reasons given in Section 3.2. That is, the exact number of the participants with prior MIs before randomization in the entire randomized population is unknown. Therefore, it is not possible to check whether these participants that should have been excluded from the analysis will alter the findings. The PHS group should reexamine their data and address this issue.

Statistical significance claimed in the PHS report regarding fatal MI or the combined endpoint consisting of nonfatal MI, nonfatal stroke, and cardiovascular deaths was overstated. As explained in Section 3.3, the study did not provide conclusive evidence regarding the benefits of aspirin use on these endpoints.

The aspirin group appears to have higher incidences of strokes than the placebo group. In addition, the aspirin group reported a significantly higher incidence of bleeding, as compared to placebo.

Table 1. Confirmed Deaths According to Treatment Group

CATEGORY OF DEATHS (9th ICD CODES)	ASPIRIN	PLACEBO	RELATIVE RISK	95% CONFIDENCE INTERVAL	P-VALUE
Total cardiovascular deaths†	81	83	0.96	0.60-1.54	0.87
Acute myocardial infarction (410)	10	28	0.31	0.14-0.68	0.004
Other ischemic heart disease (411-414)	24	25	0.97	0.60-1.55	0.89
Sudden death (798)	22	12	1.96	0.91-4.22	0.09
Stroke (430,431, 434,436)‡	10	7	1.44	0.54-3.88	0.47
Other cardiovascular (402,421, 424,425,428,429, 437,440,441)	15	11	1.38	0.62-3.05	0.43
Total noncardiovascular deaths	124§	133	0.93	0.72-1.20	0.59
Total deaths with confirmed cause	205	216	0.95	0.79-1.15	0.60
Total deaths¶	217	227	0.96	0.80-1.14	0.64
(person-years)	(54894.6)	(54864.2)			

† For this analysis, all fatal cardiovascular events are included, regardless of prior nonfatal event.

‡ This includes ischemic: 3 aspirin, 3 placebo; hemorrhagic: 7 aspirin, 2 placebo; unknown etiology: 0 aspirin, 2 placebo.

§ This includes the one death due to gastrointestinal hemorrhage

¶ Additional events that could not be confirmed due to unavailability of records included 23 deaths (12 in aspirin and 11 in placebo), of which 11 were suspected to be cardiovascular (7 in aspirin and 4 in placebo) and 12 noncardiovascular (5 in aspirin and 7 in placebo).

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Mathematical Statistician

Tie-Hua Ng, Ph.D.
Mathematical Statistician

This review consists of 9 pages and 7 tables.

Concur: Dr. Chi 9/11/89

for Dr. Dubey SEN 9/11/89

cc: ✓IND No. 17,275
HFD-180
HFD-180/Dr. Fredd
HFD-180/Dr. Triantas
HFD-180/Mr. Hassall
HFD-344/Dr. Lisook
HFD-713/Dr. Dubey
HFD-713/Dr. Chi
HFD-713/Dr. Hung
HFD-713/Dr. Ng
Chron.

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Table 2. Confirmed* Cardiovascular End Points in the Aspirin Arm of the Physicians' Health Study, According to Treatment Group

END POINT	ASPIRIN	PLACEBO	RELATIVE RISK	95% CONFIDENCE INTERVAL	P-VALUE
Myocardial infarction					
Fatal	10	26	0.34	0.15-0.75	0.007
Nonfatal	129	213	0.59	0.47-0.74	<0.00001
Total	139	239	0.56	0.45-0.70	<0.00001
(person-years)	(54560.0)	(54355.7)			
Stroke					
Fatal	9	6	1.51	0.54-4.28	0.43
Nonfatal	110	92	1.20	0.91-1.59	0.20
Total	119	98	1.22	0.93-1.60	0.15
(person-years)	(54650.3)	(54635.8)			

*Additional events that could not be confirmed due to unavailability of records included 17 myocardial infarctions (10 in aspirin and 7 in placebo) and 11 strokes (3 in aspirin and 8 in placebo).

Table 3. Subgroups of Strokes Classified as Ischemic or Hemorrhagic, According to Severity*

TYPE OF STROKE	ASPIRIN	PLACEBO	RELATIVE RISK	95% CONFIDENCE INTERVAL	P-VALUE
Ischemic etiology					
Mild	69	61	1.13	0.80-1.60	0.48
Moderate, severe, or fatal	21	20	1.05	0.57-1.95	0.88
Unknown severity	1	1			
Total	91	82	1.11	0.82-1.50	0.50
Hemorrhagic etiology					
Mild	10	6	1.67	0.61-4.57	0.32
Moderate, severe, or fatal	13	6	2.19	0.84-5.69	0.11
Total	23	12	2.14	0.96-4.77	0.06
Unknown etiology					
Mild	2	1			
Moderate, severe, or fatal	1	2			
Unknown severity	2	1			
Total	5	4			
Total	119	98	1.22	0.93-1.60	0.15

* Severity was defined as follows: mild - impairment not affecting functioning; moderate - functional impairment; and severe - a major change in life style or dependency.

Table 4.

Results from Logistic Regression
Aspirin Effect Controlling for*:
Beta Carotene, Age, Cigarette Smoking,
Diabetes, Family History of MI,
Blood Pressure, Alcohol Consumption,
Exercise and Body Mass Index

Endpoint	Beta	Standard Error	Chi-Square	p	RR	LL	UL
MI	-0.5967	0.1185	25.35	0.0000	0.5506	0.4365	0.6946
Stroke	0.0971	0.1531	0.40	0.5260	1.1020	0.8162	1.4878
CV Death	-0.0439	0.1836	0.06	0.8108	0.9570	0.6677	1.3716
Death	-0.1039	0.1174	0.78	0.3765	0.9013	0.7159	1.1347
Nonfatal MI, Nonfatal Stroke and CV Death	-0.2938	0.0806	10.66	0.0009	0.7454	0.6264	0.8869

* Cholesterol was not included because approximately two thirds of the sample did not provide a baseline cholesterol level.

Table 5. Risk of Total Myocardial Infarction Associated With Aspirin Use, by Level of Coronary Risk Factors

	Aspirin		Placebo		RR	
	MI/Total	%	MI/Total	%		P-Value
Age (Years)						
40-49	27/ 4527	0.6	24/ 4524	0.5	1.12	0.676
50-59	51/ 3725	1.4	87/ 3725	2.3	0.58	0.002
60-69	39/ 2045	1.9	84/ 2045	4.1	0.46	0.00004
70-84	22/ 740	3.0	44/ 740	6.0	0.49	0.006
Smoke Cigarettes						
Never	55/ 5431	1.0	96/ 5488	1.8	0.58	0.001
Past	63/ 4373	1.4	105/ 4301	2.4	0.59	0.0007
Current	21/ 1213	1.7	37/ 1225	3.0	0.57	0.039
Diabetes Mellitus						
Yes	11/ 275	4.0	26/ 258	10.1	0.39	0.008
No	128/10750	1.2	213/10763	2.0	0.60	<0.00001
Parental History of MI						
Yes	23/ 1420	1.6	39/ 1432	2.7	0.59	0.042
No	112/ 9505	1.2	192/ 9481	2.0	0.58	<0.00001
Cholesterol Level (mg/100 ml)						
< 159	2/ 382	0.5	9/ 406	2.2	0.23	0.046
160-209	12/ 1587	0.8	37/ 1511	2.5	0.29	0.0002
210-259	26/ 1435	1.8	43/ 1444	3.0	0.61	0.042
> 260	14/ 582	2.4	23/ 570	4.0	0.59	0.058
Diastolic Blood Pressure (mm Hg)						
< 69	2/ 583	0.3	9/ 562	1.6	0.21	
70-79	24/ 2999	0.8	40/ 3076	1.3	0.61	0.010
80-89	71/ 5061	1.4	128/ 5083	2.5	0.55	0.00005
> 90	26/ 1037	2.5	43/ 970	4.4	0.56	0.018
Systolic Blood Pressure (mm Hg)						
< 109	1/ 330	0.3	4/ 296	1.4	0.22	
110-129	40/ 5072	0.8	75/ 5129	1.5	0.52	0.0006
130-149	63/ 3829	1.7	115/ 3861	3.0	0.55	0.0001
> 150	19/ 454	4.2	26/ 412	6.3	0.65	0.160
Alcohol Use						
Daily	26/ 2718	1.0	55/ 2727	2.0	0.45	0.001
Weekly	70/ 5419	1.3	112/ 5313	2.1	0.61	0.001
Rarely	40/ 2802	1.4	65/ 2897	2.2	0.63	0.022
Vigorous Exercise at least Once/Week						
Yes	91/ 7910	1.2	140/ 7861	1.8	0.65	0.001
No	45/ 2997	1.5	92/ 3060	3.0	0.49	0.00009
Body Mass Index (kg/m)						
< 23.0126	26/ 2872	0.9	41/ 2807	1.5	0.61	0.052
23.0127-24.4075	32/ 2700	1.2	46/ 2627	1.8	0.68	0.095
24.4076-26.3865	32/ 2713	1.2	75/ 2803	2.7	0.44	0.00006
> 26.3866	49/ 2750	1.8	78/ 2776	2.8	0.63	0.013

Table 6. Side Effects by Treatment Group

CATEGORY OF EVENTS (9th ICD CODES)	ASPIRIN N	ASPIRIN %	PLACEBO N	PLACEBO %	P-VALUE
Gastrointestinal symptoms (except ulcer)	3843	34.8	3779	34.2	0.48
GI discomfort (535)	2882	26.1	2823	25.6	0.45
Other non-infectious disorders of the digestive tract (536,537.8,537.9)	345	3.1	288	2.6	0.02
Miscellaneous symptoms of the digestive tract (533.123,787,789.0)	2384	21.6	2405	21.8	0.75
Upper GI ulcers	169	1.5	138	1.3	0.08
Esophageal ulcer (530.2)	11	0.1	6	0.05	0.23
Gastric ulcer (531)	25	0.2	15	0.1	0.11
Duodenal ulcer (532)	46	0.4	27	0.2	0.03
Peptic ulcer (533)	156	1.4	129	1.2	0.11
Gastrojejunal (534)	3	0.03	4	0.04	0.70
Bleeding problems	2979	27.0	2248	20.4	<0.0001
Easy bruising (459)	1587	14.4	1027	9.3	<0.0001
Hematemesis (578.0)	38	0.3	28	0.3	0.22
Melena (578.1)	364	3.3	246	2.2	<0.00001
Nonspecific GI bleeding (578.9)	440	4.0	422	3.8	0.55
Epistaxis (784.7)	862	7.8	640	5.8	<0.0001
Other bleeding* (599.7,958.2)	724	6.6	596	5.4	0.0004

*29% were related to shaving or brushing teeth (32% aspirin, 27% placebo), and 72% were hematuria (70% aspirin, 75% placebo)

Table 7. Stroke
(Stratified by 40-49 vs. 50-84)

	ASA	Placebo	rr	P	CI
Nonfatal Stroke					
40 - 49	6	7	0.80	0.780	(0.171, 3.760)
50 - 84	106	84	1.26	0.110	(0.948, 1.683)
	Chi-Square for Heterogeneity			0.458	p=0.499
Fatal Stroke					
40 - 49	1	0			
50 - 84	6	7	0.85	0.782	(0.279, 2.616)
Total Stroke					
40 - 49	7	7	0.95	0.999	(0.000, x.xxx)
50 - 84	112	91	1.23	0.140	(0.934, 1.624)
	Chi-Square for Heterogeneity			0.143	p=0.706
Ischemic Stroke					
40 - 49	4	6	0.64	0.526	(0.165, 2.513)
50 - 84	87	76	1.15	0.388	(0.842, 1.558)
	Chi-Square for Heterogeneity			0.691	p=0.406
Hemorrhagic Stroke					
40 - 49	3	1			
50 - 84	20	11	1.82	0.106	(0.881, 3.754)
	Chi-Square for Heterogeneity			0.221	p=0.638

Please attached addendum to MO's review dated 9-11-89

MEDICAL OFFICER'S REVIEW OF IND 17-275
(Aspirin)

10/4/89

E R R A T A

P. 5, beginning of 5th paragr., change:

"Aspirin reduced the incidence of non-fatal reinfarction.....events by 25%."

to

"Aspirin reduced the incidence of non-fatal reinfarction by 49%, of non-fatal stroke by 46%, of total vascular mortality by 23% and the incidence of any vascular event by 28%".

P. 6, paragr. 1, line 10: insert a"<" sign after "p (p<0.05)."
line 12: erase ">" after "0.05."

paragr. 2, line 12: change "Table 8" to "Table 7a"
line 14: change "33%" to "32%".

P. 7, last paragr., 3rd line: change "2B" to "2Ad".

P. 15, last paragr., line 1: change "41" to "40".

P 17, last paragraph, line 2 from bottom: insert "primary" after "prevention of" and before "heart attacks" to read "on the prevention of primary heart attacks is premature."

P. 19, first paragr., last line: add a "c" in "cardiovascular"

Insert Table 7a after Table 7.

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Table 1a. Aspirin in Primary Prevention (U.S. Physicians' Health Study and British Doctors' Trial Results)

	Reduction (% ± SD)		
Endpoint	U.S. Physicians' Health Study	British Doctors' Trial	Overview of both trials
Nonfatal MI	39 ± 9	3 ± 19	32 ± 8
Nonfatal stroke	*†19 ± 15	†13 ± 24	†18 ± 13
Total cardiovascular death	2 ± 15	7 ± 14	5 ± 10
Any vascular event	18 ± 7	4 ± 12	13 ± 6

*† denotes a nonsignificant increase in stroke among aspirin-allocated subjects

DIVISION OF GASTROINTESTINAL AND COAGULATION DRUG PRODUCTS
MEDICAL OFFICER'S REVIEW

SEP 11 1989

IND: 17-275

DRUG: Aspirin

SPONSOR: Charles Hennekens, MD.
Channing Laboratory
Dept. of Medicine
Harvard Medical School
Boston, MA

DATE OF SUBMISSION: June 9, 1989

DATE RECEIVED BY MEDICAL OFFICER: June 26, 1989.

CONTENTS: This submission contains a prepublication copy of the Final Report of the Aspirin Component of the Ongoing Physicians' Health Study and also copies of two review articles. The submission further contains explanations about the study: copies of the Questionnaires which were sent to the participants, description of the procedures used, definitions of the variables, description of the methods of monitoring side effects, description of the methods of analysis and a copy of the protocol.

FIRST PART OF REVIEW

DATE COMPLETED: July 10, 1989

1. The Physicians Health Study Final Report by Hennekens et al (Part II of the submission). This report is scheduled to appear in the July 20 issue of the New England Journal of Medicine. The typescript is the same as the one which was submitted to FDA last March, except for several changes in the numbers of Table 5 (Side Effects). These changes are small and do not substantially change anything. This study has been reviewed before, but in order to refresh our memories the following synopsis is provided:

   The study was designed to test two primary prevention hypotheses: whether low-dose aspirin (325 mg) every other day reduces total cardiovascular mortality (and total mortality), and whether beta-carotene (50 mg) on alternate days decreases the incidence of cancer.

   All male physicians 40-84 years old residing in the U.S. at the beginning of the study (1983), were sent questionnaires and invitations to participate. Of the 112,528 physicians who were contacted, 59,285 responded. Physicians who had a personal history of MI, stroke, TIA, cancer, current liver or renal disease, peptic ulcer, gout, contraindications to aspirin, or were currently using aspirin or other platelet active drugs or vit. A supplements, were excluded.

Of the 59,285 physicians who responded 33,223 were found to be eligible to enter the study. One third of these physicians, however, was eliminated during an 18-week pilot study because of non-compliance or because of serious side effects caused by aspirin. Thus the number of physicians who were included in the final study was reduced to 22,071. The participants were then randomized using a 2 x 2 factorial design under double-blind conditions into 4 groups:

Active aspirin, active beta carotene
Active aspirin, beta carotene placebo
Aspirin placebo, active carotene
Aspirin placebo, beta carotene placebo.

A total of 11,037 physicians were assigned to receive active aspirin and 11,034 to receive aspirin placebo. All participants were stratified by age in 10 year groups.

Every 6 months for the first year and annually thereafter the participants were sent a supply of monthly calendar packs of White tablets supplied by Bristol Myers containing aspirin (Bufferin) or aspirin-placebo to be taken on odd numbered days and Red capsules containing beta carotene or carotene placebo to be taken on even numbered days. The participants were also sent brief questionnaires about compliance and relevant outcomes (MI, other ischemic heart disease, pulmonary embolism, DVT, TIAs, diabetes, sudden death, other cardiovascular death, stroke, death from any cause, cancer etc). The study was supposed to last for an unreported number of years.

On Dec 18, 1987 the Data Monitoring Board recommended early termination of the blinded aspirin component of the trial based on "three major considerations:

a. the presence of a statistically significant ($p<0.00001$) reduction in risk of total myocardial infarction among those in the aspirin group;

b. the inability of the trial to detect any effect of aspirin on cardiovascular mortality until the year 2000 or later"; and

c. "the fact that over 85% of the participants experiencing non-fatal vascular events were subsequently prescribed aspirin, which made any finding concerning cardiovascular mortality particularly difficult to interpret."

The final report presents the results of the aspirin arm of the study as of January 25, 1988, the date the participants were informed about their aspirin assignment. By that date the mean duration of the study was 60.2 months (45.8-77.0 mos). The reported consumption of aspirin or other platelet active drugs was 85.71% in the aspirin group and 14.23% in the placebo group. A total of 1,269 participants (624 and 645 respectively) were taking enteric coated preparations.

All available information was collected through the Questionnaires, letters, postcards and telephone calls. The diagnoses were documented by hospital records, death certificates or observers' impressions for deaths outside hospitals. They were then confirmed by the End Points' Committee (two internists, a cardiologist, and a neurologist) with all members blinded to treatment assignment. When written consent or the relevant records were not obtained, a reported event was not considered confirmed and was not included in the analysis.

The diagnoses were converted to the appropriate International Classification of Disease (ICD-9) codes and dated. The earliest date was checked against the date of randomization and the analyses were based only on events whose first report was post-randomization.

The results are shown in Tables 1-3. The investigators reported that there were 139 MIs among the aspirin participants and 239 among those receiving placebo suggesting that aspirin reduced the relative risk for MI to 0.56, ($p<0.00001$) compared to placebo. Ten of the aspirin and 26 of the placebo MIs were fatal ($p=0.007$).

Regarding strokes, the results indicated that aspirin was of no help at all. There were 119 events in the aspirin group and 98 in the placebo group, i.e. aspirin increased the relative risk for stroke in general by 1.22 ($p=0.15$). Ten of the aspirin and 7 of the placebo episodes (Table 3) were fatal ($p=0.47$). Although most of the strokes were of ischemic etiology aspirin did not seem to reduce their incidence. There were 69 ischemic strokes in the aspirin group and 61 in the placebo group.

For hemorrhagic strokes aspirin proved to be harmful. There were 23 episodes of hemorrhagic stroke in the aspirin group and 12 in the placebo group i.e. there was an increase in relative risk by a factor of 2.14 ($p=0.06$), which was more pronounced in moderate/severe and fatal strokes (13 vs 6, $p=0.11$).

The placebo fared better regarding also sudden death. There were 22 sudden deaths in the aspirin group and 12 in the placebo group ($p=0.09$) indicating an increase in relative risk by a factor of 1.96, almost double. No significant differences were found regarding "other cardiovascular deaths" (Table 3; 15 vs 11) or the total number of cardiovascular deaths (81 vs 83), or regarding the number of noncardiovascular deaths (124 vs 133) or the number of total deaths (217 vs 227 respectively; Table 3).

In order to focus more attention on the effectiveness of aspirin, Hennekens et al combined all nonfatal MIs, all nonfatal strokes and all cardiovascular deaths into one endpoint. They found that there were 307 such events in the aspirin group and 370 in the placebo group (rel. risk decrease: 0.82; $p=0.01$).

The investigators further analysed the effect of aspirin on the incidence of MI in subjects with various risk factors (smoking, high blood pressure, body weight, age, cholesterol levels, etc, see Table 4). They found that aspirin significantly reduced the risk of MI in people over the age of 50 ($p=0.02$). They further found that "for cholesterol, the beneficial effects of aspirin on MI were apparent in all strata but appeared greatest

at lower levels (p=0.04)". With respect to the other factors, there was no consistent effect on the association between aspirin and MI, stroke or cardiovascular mortality, except for cigarette smoking and cardiovascular mortality. The investigators claim that aspirin reduced the risk among non smokers (p=0.18), while it increased the risk among current smokers (p=0.20). However, the data referring to these effects are not reported.

Side Effects: The reported side effects were mainly gastrointestinal (Table 5). No significant differences in the overall occurrence of these effects between aspirin and placebo (34.8% vs 34.2% excluding ulcer) were observed. This was probably due to the fact that aspirin was used at a low dosage (325 mg every other day) plus the fact that subjects sensitive to aspirin were weaned out during the initial pilot study and that some of the participants were supplied with enteric coated preparations. Significant differences were observed, however, in the incidence of duodenal ulcer (0.4% vs 0.2%; p=0.03), the incidence of "other non-infectious diseases of the digestive tract" (3.1% vs 2.6%; p=0.02) and in bleeding problems generally (easy bruising, hematemesis, melena, epistaxis, or other bleedings). Twenty-seven percent of the aspirin participants reported bleeding compared to 20% of the placebo participants (p<0.0001-0.00001). Both the frequency and the severity of the side effects attributed to aspirin were far lower than those reported in previous studies. Nevertheless 48 of the aspirin and 28 of the placebo participants (p=0.02) required transfusions and one aspirin participant died from G.I. bleeding.

2. The Review Articles

A. "Aspirin and Other Antiplatelet Agents in the Secondary and Primary Prevention of Cardiovascular Disease" by Hennekens et al (Part III of the submission). This is a review paper and has been accepted for publication at Circulation.

This paper reviews briefly:

a) The mechanism of action of aspirin.

b) Aspirin Therapy for Secondary Prevention of Cardiovascular Disease.

In this section Hennekens et al discuss the conclusions of an overview (or "meta-analysis": Anti-Platelet Trialists' Collaboration. Secondary Prevention of Vascular Disease by Prolonged Antiplatelet Treatment, Br. Med. J. 296:320-331, 1988) of the results of 25 randomized trials with various antiplatelet agents (aspirin, dipyridamole, sulfinpyrazone or suloctidil either alone or in combination) in patients with prior cerebrovascular or coronary heart disease. These studies included a total of 29,000 individuals. The authors stress the fact that each of these trials were too small to yield statistically stable results. Their results analysed together, however, in the meta-analysis have yielded a more stastistically stable estimate with less variability and have minimized "the introduction of selection biases". The authors conclude that the combined results of all these studies have shown that antiplatelet therapy reduces the risk for subsequent nonfatal MI

by 32%, the risk for subsequent nonfatal stroke by 27%, the risk for total cardiovascular mortality by 15% and the risk for ever developing a subsequent important vascular event (any of the above 3 categories) by 25%. All these reductions in risk were found to be highly significant ($p<0.0001$) and were independent of the "characteristics of the study populations at entry" i.e. whether the patients had suffered a prior coronary or cerebrovascular event.

Direct and indirect comparison of aspirin to sulfinpyzazone (Table 6, Table 2 of the review) by the meta-analysis indicated that there were no significant differences between these two drugs regarding the prevention of important vascular events. It also indicated that combined treatment with aspirin and dipyridamole is no better than aspirin alone (something we knew all along).

These studies showed further that aspirin dosages of 0.3 g/day were not less effective than dosages of 0.9-1.5 g/day in reducing the incidence of cardiovascular events.

c) Aspirin Therapy in Suspected Evolving MI.
This part of the review summarizes the results of ISIS-2 (the Second International Study of Infarct Survival). In this study a little over 17,000 patients with suspected AMI were randomized to be treated either with a single dose of 1.5 million units of streptokinase i.v. over 60 min, or with 162 mg/day of oral aspirin for one month or with both aspirin and streptokinase or with neither. All arms of the trial were placebo controlled. Five weeks after randomization the results regarding aspirin were as follows:

Aspirin reduced the incidence of non-fatal reinfarction by 49%, of non-fatal stroke by 46%, of total vascular mortality by 23% and of any vascular event 28%. Regarding vascular mortality it did not matter whether the patients were receiving heparin or not. Aspirin was equally effective in reducing mortality in patients who were receiving heparin (s.c. or i.v.) and in those who were not receiving it. This finding suggests that heparin is not a sufficient antithrombotic treatment in acute MI. Hennekens et al compared these results of short-term antiplatelet treatment with the results of long-term treatment of patients with a history of MI and found that the general pattern was "quite similar" (Table 7, Table 4 of the review).

In ISIS-2 there were no significant differences between the aspirin and the placebo group regarding major bleeds or non vascular deaths. However, aspirin seemed to aggravate the increase in hemorrhagic strokes caused by streptokinase. Hannekens et al believe that this aggravation "is outweighted by the protective effects of aspirin against occlussive stroke and of stroke as a whole."

d) Aspirin Therapy in Primary Prevention. In this section of the review, the authors summarize the results of the U.S. Physicians Health Study (see item 1 of the present MOR review) and the British Doctors' Trial (Peto et al. "Randomized Trial of prophylactic daily aspirin in British male Doctors". Br Med J 296: 313-6, 1988).

In the latter study 5,139 male British Physicians, aged 50-79 years, were randomized either to receive 0.5 g of aspirin daily or to avoid aspirin and all products containing aspirin, for 6 years. There was no placebo control and the study was open. The results indicated no significant differences between the groups regarding total vascular mortality, nonfatal MI, or nonfatal stroke or the combined total vascular events. As in the U.S. study, disabling strokes were more common (19.1 vs 7.4/10,000 man years) among the physicians allocated to aspirin and in the British study the difference was statistically significant $p < 0.05$. The authors of the review consider this difference not "clearly" statistically significant. They claim that p was = 0.05. They believe that this result may be due to the fact that the British study was open without placebo control and the results may reflect "some bias introduced by the subjective nature of the assessment of residual impairment." Only TIAs, migraine and certain types of muskuloskeletal pain were reported significantly less often in the aspirin group in the British study.

Per addendum 3 10-4

Hennekens et al commented further on the differences of the two studies. The US. study was double-blind, placebo controlled, with a dosage of 325 mg every other day and involved 21,000 physicians. The British study, on the other hand, was open, had no placebo control, it used a dosage of 500 mg of aspirin/day and included a little over 5,000 physicians. The percentage of physicians who took aspirin or other platelet active drugs in the U.S. study was 86% in the aspirin group, 14% in the placebo group and the between groups difference was 72%. The respective percentages for the British study as reported in the review were 70%, 2% and 68%) i.e. the between groups difference in compliance was pretty much the same. The authors combined the results of the two physician studies and reported (Table 7a, Table 5 of the review article) that the overall reduction in nonfatal MI was a highly significant 32% ($p < 0.0002$), the reduction in "any vascular event" was 13%, and the reduction in total cardiovascular death 5%. The 18% increase in stroke was not discussed in the text.

e) The Side Effects of Aspirin. The authors refer to the UK-TIA Study (Br Med J 296:316-20, 1988) where indigestion, nausea, heartburn and GI bleeding in general were found to be dose related in the range of 0.1 to 1.2 g/day. (The effect of aspirin on platelet aggregation has been found to be independent of dose within this range). Constipation and paradoxically serious G.I. bleeding were not found to be dose-related in the UK-TIA study.

The authors further discuss the fact that there was no significant difference in the number of patients with side effects between the aspirin and the placebo group in the U.S. Physicians' Study. As discussed earlier the lack of difference was attributed to the fact that the dosage was small and on alternate days and that the physicians who were unable to tolerate the drug were excluded during the prerandomization run-in. The authors said nothing about the highly significant differences between aspirin and placebo which were observed regarding bleeding (Table 5 of the Physicians' Study).

f) Current Knowledge on Aspirin and Cardiovascular Disease.
The authors suggest that the reduction in the incidence of primary MI which was observed in the U.S. Physicians' Study "taken together with the similar-sized reduction in the high risk subjects in the secondary prevention trials", justify a general conclusion that aspirin can reduce the incidence of myocardial infarction in a wide range of circumstances in men. Regarding women the authors point out that both the overview of the 25 aspirin trials and ISIS-2 demonstrated significant protection from cardiovascular events as in men and "it is reasonable to hope that, at least among women who are old enough to be at appreciable risk of having a first MI, aspirin might be protective against this". However, the authors conclude, there is no direct evidence that this could be achieved and suggest that the only reliable way to assess this question directly would be a large primary prevention trial.

g) Aspirin as an Adjunct to Management of Other Coronary Risk Factors.
The authors suggest that aspirin should be viewed as a possible adjunct, not as an alternative, to coronary risk factor management. For primary prevention, any decision to use aspirin among middle-aged and older adults should consider the cardiovascular risk profile of the patient. "In most circumstances it would be reasonable to assume that aspirin will reduce nonfatal MI by about one third, with an effect that is still favorable (but probably not as large as one third) on death from coronary heart disease. The apparent effect (of aspirin) on stroke was not favorable, perhaps because of a small number of hemorrhagic strokes, and the prescription of long term aspirin might therefore be restricted to circumstances where the incidence of MI is expected to be so high that even the moderate reduction that aspirin can be expected to produce is likely to outweigh any possible adverse effect on stroke or other conditions." Regarding secondary prevention the authors assert that there is no uncertainity. The usefulness of aspirin has been proven conclusively.

B. Prepublication copy of a review article entitled "Aspirin Prophylaxis" by the U.S. Preventive Services Task Force (a collaboration between the U.S. Government and Harvard University), to be published in the "Guide to Clinical Preventive Services." (Part I of the submission)

This article starts with the recommendation that "Low-dose aspirin should be considered for men aged 40 and over who are at significantly increased risk for MI and who lack contraindications to the drug. Patients should understand the potential benefits and risks of aspirin therapy before beginning treatment."

This recommendation is based on the results of the U.S. and British Physicians' studies for primary prevention of cardiovascular events (these studies are discussed in more detail in sections 1 and 2Ad of this MOR).

The "Aspirin Prophylaxis" review refers to the incidence of MI in the U.S. (1.5 million/year), the frequency of deaths from MI (500,000/year) and of sudden death (400,000/year) and to the cost of medical care for cardiovascular disease (80 billion for 1986). It goes on further with the pros and cons of long term aspirin treatment, its feasibility and side effects. It discusses briefly the results of the U.S. and British Physicians' studies and stresses the "significant reduction in the incidence of the fatal and non-fatal MI " which was found in the U.S. study. It plays somewhat down the effect of aspirin on stroke. It suggests that perhaps a dosage as low as 30-40 mg of aspirin/day might be sufficient. The review concludes that "low dose aspirin therapy should be considered for primary prevention in men aged 40 and over who have risk factors for MI and who lack a history of uncontrolled hypertension, liver or kidney disease, peptic ulcer disease, a history of GI or other bleeding problems or other risk factors for bleeding or cerebral hemorrhage. Patients should understand the potential benefits and risks associated with aspirin therapy before beginning treatment and they should be encouraged to focus their efforts on modifying primary risk factors such as smoking, elevated cholesterol and hypertension."

The article is prefaced by Dr. R. S. Lawrence, M.D., Chief of Medicine at Harvard Medical School and Chairman of the U.S. Preventive Services Task Force. Dr. Lawrence asserts that "the Guide is the culmination of over 4 years of literature review, debate, and synthesis of critical comments from expert reviewers. It offers the Task Force members' best judgment, based on the evidence, of the clinical preventive services that prudent physicians should provide their patients in the course of routine clinical care." He has certainly placed a lot of emphasis on the merits of this review.

3. The June 9 submission also contains the following sections:

IV. Copies of the Physicians' Study Questionnaires.

This section contains blank samples of each of the 12 questionnaires which were sent to the participants during the course of the study.

V. Description of the Procedures used in the Physicians' Health Study for following, verifying, recording, and selecting for analyses and for End Point Information.

This section specifies the steps which were taken to identify and record reported events. It also contains a description of the criteria used to identify the events.

VI. Procedures for Processing Side Effects in the Physicians Study.

A general description.

VII. A List of Definitions of Variables Used in the Final Report.

This section indicates the ICD-9 codes corresponding to the Endpoints, and to the side effects. It also shows the baseline variables. Cholesterol levels, diastolic and systolic blood pressure values were self-reported values at enrollment.

VIII. Copy of the method used to compute person/years of exposure.

This section contains computer instructions.

IX. Description of Data Analyses and Statistical Formulas.

X. A copy of the Protocol for the Physicians' Study.

According to the protocol the aspirin component of the study had two primary endpoints: total mortality and total cardiovascular mortality. The secondary endpoints were stroke, TIAs, nonfatal AMI, and "a number of other conditions".

This Protocol gives a surprising definition for TIA and stroke. TIAs according to this protocol are local neurological deficits "lasting for up to one week in duration". "A stroke has the same criteria but with symptoms lasting one week or more."

SECOND PART OF THE REVIEW

DATE COMPLETED: September 1, 1989

Review of the Records of the Physicians' study at 55 Pond Ave, Brookline, MA, a Subdivision of Channing Laboratories, Harvard University.

Dr. Ti Ng, statistician from the Division of Biometrics, and I visited Dr. Hennekens' Research Facility at Brookline, MA, on July 19, 20, and 21. I visited this Facility again alone on July 24 and 25 to review more records.

We met Dr. Hennekens and his associate, Mrs. Fran Stubblefield, Systems Analyst and Head of the Data Processing Department of the Research Group. We were given a tour of the Facility and were introduced to the other members of the group. We then discussed the study with Dr. Hennekens and Mrs Stubblefield. We found them, as well as the rest of the group, very cooperative. They allowed us to inspect the records and were helpful in all respects.

The time allocated for my visit was inadequate to review all the records. I chose therefore to review the records of those categories where significant and nearly significant differences between aspirin and placebo were found i.e. I checked the files of the patients who had fatal and non-fatal MIs and also the records of the patients who had died from sudden death. There was no time to check the records of the patients who had suffered strokes.

I concentrated my attention on the important aspects of the study i.e. to verify or exclude the occurrence of acute MIs. I may have missed other events which were also recorded in these files. It is also possible that I did not get all the facts for certain MI cases. There is a limited amount of data one can go through within a limited period of time, even if one works 9-13 hours/day.

I did the review of all the records blindly. Mrs. Stubblefield gave me the code for the participants who died on Tuesday, July 25, at 9:30 P.M. before I left the Research Facility. She promised to mail the code for the non-fatal MIs the next morning.

I received this code on August 15 long after I had already made my conclusions regarding each individual case.

Non-Fatal MIs:

It appears that there were at least 512 participants who reported that they had a non-fatal AMI during the study. Of these patients 287 had been randomized to placebo and 204 to aspirin. There were 21 additional patients, at least, (Table 8) for whom the drug assignment has not been revealed. These patients were not included in the code lists which were sent to us from Brookline, although I had seen files for these patients there. There is the possibility that these patients suffered their MIs after the termination of the aspirin arm of the study, and were thus ineligible to be included in the analysis.

The list of the disconfirmed MIs which was sent to FDA by Dr. Hennekens, indicates that 74 of the placebo and 75 of the aspirin cases were not confirmed. Fourteen of these cases, 6 placebo, 6 aspirin and 2 of unknown assignment, had no hospital or physician's records, thus there was no evidence to confirm their reported AMIs. However, one of these cases, placebo # 3669937 was treated as confirmed, probably by mistake, and was included in the analysis. Two additional cases, placebo case # 1538887 and aspirin case # 2721522, had no hospital or physician's records either. However, Dr. Goldhaber, the cardiologist of the study, told me that he was able to discuss these cases with the personal physicians of the patients on the telephone and became convinced that these patients had typical symptoms of the disease. He had summarized this information in each patient's file.

The remaining cases were disconfirmed because they did not meet the criteria for the diagnosis of an AMI i.e. they did not have at least two of the following criteria: chest pain, increase in the serum levels of cardiac enzymes, or an EKG tracing showing an infarction pattern. Dr. Goldhaber told me that old MIs were not counted for the study. Evidence from EKG, angiography, thallium or technetium scans or from other tests alone was disregarded except if there was also evidence that the patient had experienced pain or an increase in cardiac enzymes or he had a previous EKG tracing or scintigraphic scan that was different from the one under evaluation.

In the overwhelming majority of cases I found that the evaluations of the End Points' Committee were justified. I disputed some evaluations and I discussed my objections with Dr. Goldhaber. We finally agreed on everything except in:

Aspirin patient # 1405888 was bypassed for unstable angina. He had pain and his CPK rose to 548 and 600 (CPK-MB 63 and 54) units. His case was disconfirmed. I believe that his MI should have been confirmed. He had two of the typical criteria of an MI: chest pain and a rise in cardiac enzymes.

I am still confused with Dr. Goldhaber's explanation regarding two other cases. Aspirin Pt #3702993 had an abnormal EKG and an increase in CPK (114->176->1020->1016->558 units; I missed the CK-MB values) during CABG or shortly thereafter but his MI was disconfirmed. Dr. Goldhaber explained that the increase in CPK was due to the CABG. However, when I discussed case #1729580 where the patient had also been bypassed and his CPK had increased to 416 and 485 (CK-MB to 50 and 54) units he said that the increase in the CPK in this case could not be due to CABG. I may have missed something here. This AMI had been ruled out by the patient's physicians but not by the study. This case has only academic significance now. It was not included in the analysis, perhaps for other reasons.

In my notes I have marked down that placebo cases #3793404 and #4222034 had been disconfirmed by the study and I had found these evaluations justified. However, when we received the code I noticed that these cases were treated as confirmed and were included in the analysis.

To complete the review of this section, I did not see the record of placebo pt #3702270 because he had died and his file was kept in another section. The record of aspirin pt #2202155 was in Spanish, the print was very faint and I could not get anything out of it.

To summarize the review of this section the records I saw at the Brookline Research Facility support the results presented in the NEJM 1989; 321; 129-35, regarding non-fatal AMIs. Even if we include aspirin patients #1405888 and 3702993 and exclude placebo patients #3669937, 3793404, and 4222034, still the difference between aspirin and placebo must be highly significant:

There were 210 cases of placebo vs 131 cases of aspirin.

It is my impression that the evaluation of each case by the investigators of this study was done in a careful and unbiased way. The evaluations which I had doubts about at the beginning were as much in favor of aspirin as they were against it.

Deaths from AMI.

I found records for 36 of the 38 patients which were classified in this category. I did not see records for aspirin cases #1416987 and 3396970.

Twenty-eight of these patients had been randomized to placebo and 10 to aspirin. One of the placebo patients, #1841300, had died of stroke (intracranial hemorrhage) while another, #3151302, also a placebo patient, had died suddenly at home without any known symptoms. No physician had attended his death or saw him during his final days or hours and no autopsy was performed. Strictly speaking the occurrence of a fatal MI was not confirmed in this patient. The exclusion of these two patients must reduce the number of the placebo patients with confirmed MIs to 26.

Dr. Ng helped me in the review of this group of patients by checking the death certificates and the discharge notes of about 1/2 of the patients. I have summarized the essential findings from the records of this group in Table 9. I have listed patients #1841300 and 3151302 at the end of the placebo list.

Fourteen placebo patients (Nos. 3-5, 7, 9, 13, 16-19, 22, 23, 25, and 26) and four of the aspirin patients (Nos. 3, 6, 7, and 10) had two or all three of the typical criteria of an AMI (chest pain, rise in cardiac enzymes, characteristic EKG pattern(s)) and were easily diagnosed that they had died from an acute MI.

Of the remaining patients, four placebo (listed in Table 9 as Nos 1, 6, 8, and 12) and two aspirin patients (Nos 1 and 8) were found dead. At least 3 other placebo (Nos. 2, 15, and 20) and two aspirin (Nos. 4, and 5) patients had collapsed suddenly. These patients had either an autopsy or they had survived long enough to be admitted to an emergency room and be diagnosed as dying or having died from an AMI.

Placebo cases Nos. 10, 11, 14, 21, and 24 did not have the necessary typical criteria to be characterized as AMIs. Nevertheless, these patients had other atypical symptoms or were subjected to procedures which made the diagnosis of an AMI possible. Thus patient No. 10 (#2345919) was diagnosed as having an AMI during CABG. He also had tachycardia and fibrillation i.e. arrhythmias known to occur in MI patients. Patient 11 (#2709793) in addition to a diagnostic EKG, had arrhythmia and acute pulmonary edema. Patient No. 21 (3726797) had indigestion, sudden collapse and an EKG indicative of an extensive anterolateral MI. Patient No. 24 (#4242965) had chest pain and arrhythmia compatible with AMI (ventricular tachycardia, atrial fibrillation,

PVCs, LBBB). Patient No. 14 (#3083799) must also be mentioned here. No coronary thrombosis was found at his autopsy. He was not witnessed to have clinical symptoms characteristic of MI and had no diagnostic EKG (he had collapsed suddenly in full cardiac arrest). This patient, however, had severe coronary atherosclerosis with marked narrowing of the LAD and circumflex arteries shown by autopsy. Considering that spontaneous thrombolysis has been reported to occur in many AMI cases, I have no objection to the classification of this case as an AMI.

In summary the records included in this section provide evidence that 26 placebo patients had died from acute MIs. One additional placebo patient had died from stroke and another from "sudden death". This section also included the records of 8 aspirin patients who had died from acute MIs. The records of two additional aspirin patients who had also died from acute MIs were not included in this section. The net sum was:

Acute MIs:	placebo 26, aspirin 10,
Strokes:	placebo 1,
"Sudden Death":	placebo 1.

Sudden Deaths:

This category included records from 34 patients (Table 10). Twelve of these patients had been randomized to placebo and 22 to aspirin. Generally, very little information was available regarding these patients. It appears that most of them (29) had been found either dead or unconsious and died shortly after they were found.

Only 4 of the patients (placebo No. 2 and aspirin Nos. 2, 12 and 17) who were found dead or collapsed had been subjected to an autopsy. Acute MI was found as the cause of death at the autopsy of aspirin patient #3129252 (No. 17 in Table 10). Copy of the autopsy report was not included in the files or I may have missed it because the records of this patient were written in Spanish (this patient lived in Puerto Rico). However, it was reported clearly that AMI was found (Infarcto Agudo del Miocardio) as the cause of death. This patient should have been included with the MI patients.

Signs of fresh MIs were not found in the other autopsies. However, one of them (aspirin case #2652327, No. 12 in Table 10) showed "moderate-severe 3 vessel atherosclerosis with apparent myocardial ischemia in a patient with right and left myocardial hypertension and extensive old septal scarring." This case should be considered as much as an AMI as was placebo case #3083799 listed in Table 9 as case #14, which I discussed earlier in the MI death category. Aspirin patient #2652327 appears actually like a more confirmable AMI case than placebo patient #3083799 because he was witnessed to have felt chest pain and vomiting before he collapsed while the latter, patient #3083799, was found already collapsed at home and nobody knows whether he had any cardiovascular symptoms at all before collapsing. It should also be mentioned here that an infarct needs some time to develop. If a patient dies instantaneously, superacutely as most of these patients did, no gross infarct would have time to develop as it happened in two cases which were confirmed by the study as fatal AMIs. The autopsy of aspirin patient No 8 (Table 9, case #3333659) who had been found dead and also the autopsy of placebo patient No 22 (Table 9, #3900939) who had survived for 1 hour after the appearance of the

symptoms, did not show any gross infarct. The only indications for the occurrence of MIs in these cases were found microscopically: variations in staining characteristics, wavy myocardial fibers with enlarged hyperchromatic nuclei or scattered foci of necrotic myocardial cells. Since it is not possible to examine the entire myocardium microscopically, it is possible to miss an acute MI all together, if there are no gross signs of necrosis.

Only 5 of the patients who were classified in the sudden death category had been examined by a physician or a nurse while they were still alive. Four of them (placebo cases #3, 5, 6, and aspirin case #18, Table 10) were found to have arrhythmias which are known to develop during myocardial infarctions (see also protocol, p. 5.14 "Atypical Symptoms"). The fifth patient aspirin #11, was reported to have had clinical symptoms (chest pain, cold feet and tiredness) before collapsing and was also found to have some increases in enzyme levels 2 days after the beginning of pain, perhaps too late to catch the peak of CPK and SGOT and too early for the peak of LDH.

All the patients for whom relevant information was available had a history of atherosclerotic cardiovascular or peripheral vascular disease or of hypertension; 9 of these patients were taking antihypertensive or MI prophylactic medication (thiazides, beta-blockers or aspirin or persantine-aspirin) in the open. Placebo patient No 10 (Table 10, case #3119950), in addition to cardiovascular disease (CVD) and hypertension (HT) had hypercholesterolemia (over 300 mg/dl), was obese and a heavy smoker. Aspirin patient, #1169359, was overweight, a smoker and had a dissection of the aorta repaired 6 years before his death. Aspirin patient No. 20 (case #3427066), had a history of hypertension and arrhythmia compatible with the presence of an MI and was grossly overweight. All these findings make the occurrence of an AMI in these patients a likely possibility. The occurrence of an AMI cannot be excluded even in the case of patient #1262270 (aspirin case No. 2 in Table 10) where no signs of atherosclerosis were found at the autopsy. It could very well have been a case of coronary spasm. This patient was target shooting in the Arizona desert when he dropped dead unwitnessed.

We should also consider that the personal physicians who knew the medical history of their patients and happened to see them during their last moments or saw them dead reached similar conclusions regarding the cause of death. The cause of death most frequently listed on the death certificates, far more frequently than other causes, was MI. Next in frequency was arrhythmia or arrhythmia due to MI, and then cardiac or cardiopulmonary arrest, atherosclerotic or hypertensive heart disease. Sudden death as a cause of death was listed only twice. Once as due to hypertensive heart disease due to aortic insufficiency and the other as due to atherosclerotic heart disease. None of the recorded causes of death is incompatible with myocardial infarction. There was no mention in the records of cardiomyopathy, mitral valve prolapse, aortic stenosis, hereditary prolongation of the Q-T interval, Wolf-Parkinson-White syndrome or digitalis poisoning. Only in one case the physician mentioned electrolyte imbalance as the cause of death but only after he thought of acute myocardial infarction first.

Conclusions: Aspirin patients No. 12 and 17 (Table 10, cases #2652327 and #3129252) should be reclassified in the confirmed AMI category.

Due to lack of adequate information or to the superacute occurrence of death, the cause of death of the remaining patients cannot be established with certainty. Nevertheless, none of the available information is incompatible with the occurrence of an acute MI in any of the cases. It is well recognized that more than 90% of the patients with acute myocardial infarctions develop ventricular arrhythmias in the first 72 hours and more than 60% of them used to die from ventricular fibrillation before reaching the hospital. It is also known that the formation of a gross infarct requires time to develop (the patient must survive for a few hours at least). Strictly speaking the term "sudden death" refers to the speed and unexpectancy of death it does not signify the cause of death. Classification of a death, in the sudden death category does not exclude the possibility that the patient actually had died from an AMI.

In reality it makes no difference whether we classify these deaths as "sudden deaths" or as "possible MIs". Even if a different mechanism than MI had been demonstrated by the study, the fact remains that the difference in the number of acute cardiovascular deaths between placebo and aspirin is not significant:

	Placebo	Aspirin
Verified AMIs:	26 (28-2)	12 (10+2)
Possible AMIs:	13 (12+1)	20 (22-2)
	39	32

Old MIs, Percutaneous transluminal Coronary Angioplasty (PTCA) and Coronary Bypass Grafting (CABG).

While I was reviewing the records of the patients with non-fatal MIs I noticed that some of these patients must have had suffered infarctions in the past, as shown by EKG tracings, thallium or technetium or gated scans or by angiography. Old infarcts were also discovered during surgery. Some of these patients as well as others had PTCAs or coronary bypasses. I did not have time to look specifically for these events. I only recorded the cases I happened to see while I was looking for data to confirm or exclude the occurrence of a reported AMI. I have summarized my findings in Tables 11, and 12.

Table 11 shows that at least 40 of the 512 (8%) patients, who had reported that they had suffered a non-fatal acute MI and whose records I saw, had evidence of an old infarct. Table 12 shows that at least 38 of these 512 (7%) patients had PTCAs (12) or CABGs (22) or both (4). The percentages are small for both the older MIs and the corrective procedures, but these cases are just a sample. I did not have time to look for all of these events specifically. Besides, I saw only the records of the patients who had reported that they had suffered an acute myocardial infarction. I did not see the records of all the participants of the study. When I recorded these events I did not know the code. These recordings were therefore done in a completely unbiased way and the sample must be representative of the true ratio of the incidence of these events in each group. The results indicate that both the patients with evidence of an older MI, as well as those who were subjected to corrective procedures, were evenly distributed among the groups.

We do not know whether these "old" infarcts were there before the patients were randomized or whether they occurred sometime during the study. Perhaps some of the information is in the records. I did not have the time to look at the dates when these scars were discovered. Even if I had, the date of the discovery does not mean much, if there is no history of symptoms or if records of earlier tests are not available.

Theoretically, if the first possibility is correct (the old infarcts occurred before randomization) the participants who had old MIs should be excluded from the analysis. The study excluded from the analysis the old MIs which were found in the records of the patients who had reported an event. However, we do not know whether these patients were also excluded from the denominator during the analysis. Similarly, there is no information of how many other participants had evidence of old MIs but were not excluded from the study because they had not reported an event. The exclusion of these patients is necessary because the objectives of this arm of the study were to evaluate the effect of aspirin on the prevention of primary cardiovascular events. If the second possibility is correct (the "old" infarcts occured during the study), the "old" MIs in the total study population should be added to the list of the non-fatal MIs. Again the entire population of the study should be checked not just the patients who had reported the occurrence of an AMI. None of these possibilities can be investigated now. EKG tracings or thallium or similar scans were not performed either at baseline or at the termination of the aspirin arm of the study. Due to the lack of such tests definite conclusions about the true incidence of myocardial infarction during the study cannot be drawn, and we cannot ascribe the outcome to prevention of a first heart attack.

The pain of an acute MI may vary from zero (silent MI) to unbearably excruciating. We should also take into consideration that most, if not all, of the patient who suffer an MI have angina and may confuse the pain of an evolving MI with the pain of an angina attack and not seek medical help, especially when the pain is slight, even moderate. Thus many of an acute MI may remain undetected and be discovered accidentally during the performance of cardiovascular tests or procedures or during an autopsy. Lack of pain does not necessarily mean lack of danger. These infarcts can be as dangerous as painful infarcts depending on their size and location and may lead to arrhythmia, shock and death as well. They may actually be more dangerous than the painful MIs because the patient does not get alarmed and seeks no help or seeks it too late.

The frequency of corrective procedures, PTCAs and CABGs, may very well indicate the degree of atherosclerosis. The more atherosclerosis advances, the more these procedures are needed. Theoretically, aspirin should delay the progression of atherosclerosis and reduce the need for corrective procedures because it inhibits platelet adhesion and aggregation. It has generally been accepted that platelets adhere to atherosclerotic plaques and initiate clotting. If the clots are not lysed, they become organized and incorporated onto the plaques. Platelets, in addition, contain a mitogen, the platelet growth factor, which stimulates the proliferation of smooth muscle cells and thus contribute to the further growth of the plaques. Theoretically, the aspirin patients of the Physicians Health Study should have had fewer PTCAs and/or CABGs than the placebo patients. My cursory observations do not indicate that such a decrease had happened. However, these observation were incomplete. The full information is in the files of the study. A relevant question was included in the Questionnaires sent to the participants at 24 months to termination and can be retrieved easily.

PTCAs and CABGs are done in order to improve the circulation of the myocardium and prevent heart attacks. knowledge of their frequency is additionally essential for the evaluation of the study findings.

SUMMARY

The time allocated for the review of the records of the Physicians' study was inadequate to allow for a complete review of each file. I was only able to review the records of the patients with non-fatal MIs and those who had died from acute MIs and "sudden deaths". Even the review of these sections was incomplete. I did not have enough time to pay attention to all the details or check again the records in cases of doubt.

The records which I reviewed, show that ingestion of one tablet of aspirin every other day significantly reduced the number of acute myocardial infarctions which were reported by a population of over 11,000 male U.S. physicians. I found small discrepancies with the published results, which, however, do not change the significance of the difference between aspirin and placebo. The number of confirmed MI cases which I found was: aspirin 131, placebo 210 compared to 129 and 213 cases respectively which were reported in the NEJM.

It seems to me that acute myocardial infarction was the most likely cause of death of the patients who had died suddenly. These deaths should be analysed together with the MI deaths. Of the 71 cases of death which belong to these categories, 39 had occurred in placebo and 32 in aspirin subjects. These numbers do not indicate a significant difference. The benefit which was observed regarding the incidence of acute non-fatal MIs was not reflected on survival. Even if we accept the investigators' conclusion that some of the patients had died from a different presumably unknown cause, the fact remains that the numbers of acute cardiovascular deaths among the aspirin and the placebo patients, whose records I reviewed, were not significantly different. Actually the destinction of a separate "sudden death" category in this study makes aspirin look worse because more aspirin than placebo patients had died from it. Most sudden deaths occur very quickly before the patient can be transferred to an emergency room or shortly thereafter and it becomes difficult or impossible to help these patients.

The seemingly contradictory results: reduction in the number of myocardial infarctions but no benefit in survival, may indicate that aspirin prevents the development of small non-fatal infarcts but it is unable to control the more serious and lethal among them. They may also indicate that the analgesic and antiinflammatory properties of aspirin may dull the pain of otherwise less painful infarctions and convert them into silent infarctions, which remain unrecognized and unreported. This hypothesis may sound ridiculous, ("low dose" aspirin cannot dull the pain of a heart attack) but we cannot exclude it without testing. The records of some of the patients which I reviewed contained evidence of infarcts. For the majority of these "old" infarcts it cannot be established whether they occurred before randomization (which raises the question of unsuitability of the patients who had them) or during the study. It is also unknown how many of the participants (irrespective of whether or not they had reported an event), had evidence of such infarcts. Since we cannot estimate the incidence of these infarcts, any conclusions regarding the beneficial effect of aspirin on the prevention of heart attacks is premature.

Primary

Per Affidavit of 20-4

The records of the patients which I reviewed further show that several participants had been subjected to corrective procedures, PTCAs and coronary bypasses, during the study. A cursory but unbiased count of these procedures indicated that their frequency was similar in the aspirin and the placebo group i.e. there was no indication that aspirin decreased the need for these procedures.

CONCLUSIONS

The U.S. physicians' study is impressive because of its magnitude and challenging because of its findings. It showed, on the one hand, that low dose aspirin can reduce the incidence of acute myocardial infarctions by one third, but on the other, this benefit was not reflected in survival or in any other way. The incidence of acute cardiovascular or of all cardiovascular deaths was not decreased by aspirin.

This study further showed that aspirin may increase the incidence of primary strokes. Although this increase was not statistically significant, it was large enough to cause concern. The increase in strokes can be explained by the antiplatelet effect of aspirin. It was unexpected, however, because previous studies on the prevention of secondary cardiovascular events, (Antiplatelet Trialists' Collaboration, ISIS-2) had shown that aspirin decreased the incidence of stroke by 27% and 46% respectively.

The study failed to confirm its primary endpoints: a reduction in total mortality and total cardiovascular mortality. Its results, however, are challenging.

This study should be duplicated in order for its results to be confirmed. To be definitive the new study should include baseline and termination EKGs and/or thallium scans or other diagnostic tests in order to a) exclude all the patients who already have cardiovascular events and b) to detect the new infarcts which will develop during the study.

The number of corrective procedures should also be recorded and evaluated.

Regarding the review articles, I think that the effect of aspirin is exagerated, especially for the prevention of primary cardiovascular events. Neither of the two physicians' studies support that much enthusiasm.

I do not think that the recommendation "low dose aspirin should be considered for men aged 40 and over ...." is justified. The physicians' Health Study did not show any benefit for men at the age of 40-49. As a matter of fact the incidence of MI was a little greater in the aspirin than in the placebo group at this age range (relative risk for the aspirin participants was 1.12; of course this difference is not significant). Even for older men the advice may be premature and unsafe. The benefit regarding the incidence of MIs which was shown in the U.S. study was not observed in the British study. Most significantly there was no significant difference in survival between the groups and the incidence of stroke and "sudden death" was higher in the aspirin group. These patients ended up with more crippling strokes and unexpected deaths. Neither the British nor the U.S. study provided evidence that aspirin has "an effect that is still favorable on death from coronary heart disease."

My experience with open studies (and I have reviewed many of them) is that most, if not all, show significant and highly significant results in favor of the evaluated drugs not against them. I do not believe that the lack of significant findings in favor of aspirin in the British study could be due to bias considering the highly publicized effectiveness of aspirin in the prevention of secondary cardiovascular events.

RECOMMENDATIONS

1. A copy of my review, properly processed through FDA channels, should be sent to Dr. Hennekens. I will appreciate his comments.

2. Dr. Hennekens should be requested to:

   a) supply FDA with a summary of all the patients who had PTCAs or CABGs during the study. This information must be in the files of the study (relevant questions were included in the Questionnaires of 24 months and subsequent ones),

   b) estimate the impact of patients with previous myocardial infarctions and those developing silent infarcts during the course of the trial on the outcome of the trial, particularly the proposed claim that aspirin prevents a first heart attack.and

   c) explain why the code for certain patients including the 21 patients which I have listed in Table 8 was not revealed to FDA.

3. Dr. Hennekens should be informed that the recommendation that "low dose aspirin should be considered for men aged 40 and over...." is not justified at this time.

E. Triantas, MD

E. Triantas, M.D.

cc:
IND 17-275
HFD-180
HFD-180/CSO
HFD-180/SFredd
HFD-180/ETriantas
HFD-180/JChoudary
HFD-180/JGibbs
ft/8/2/89/jgw/w0012T
agb/9/4/89/

9/11/89
Concur.
See transmittal letter to Dr. Hennekens.
Stephen Fredd M.D.

Table 1. Confirmed* Cardiovascular End Points in the Aspirin Arm of the Physicians' Health Study, According to Treatment Group

END POINT	ASPIRIN	PLACEBO	RELATIVE RISK	95% CONFIDENCE INTERVAL	P-VALUE
Myocardial infarction					
Fatal	10	26	0.34	0.15-0.75	0.007
Nonfatal	129	213	0.59	0.47-0.74	<0.00001
Total	139	239	0.56	0.45-0.70	<0.00001
(person-years)	(54560.0)	(54355.7)			
Stroke					
Fatal	9	6	1.51	0.54-4.28	0.43
Nonfatal	110	92	1.20	0.91-1.59	0.20
Total	119	98	1.22	0.93-1.60	0.15
(person-years)	(54650.3)	(54635.8)			

*Additional events that could not be confirmed due to unavailability of records included 17 myocardial infarctions (10 in aspirin and 7 in placebo) and 11 strokes (3 in aspirin and 8 in placebo).

Table 2. Subgroups of Strokes Classified as Ischemic or Hemorrhagic, According to Severity*

TYPE OF STROKE	ASPIRIN	PLACEBO	RELATIVE RISK	95% CONFIDENCE INTERVAL	P-VALUE
Ischemic etiology					
Mild	69	61	1.13	0.80-1.60	0.48
Moderate, severe, or fatal	21	20	1.05	0.57-1.95	0.88
Unknown severity	1	1			
Total	91	82	1.11	0.82-1.50	0.50
Hemorrhagic etiology					
Mild	10	6	1.67	0.61-4.57	0.32
Moderate, severe, or fatal	13	6	2.19	0.84-5.69	0.11
Total	23	12	2.14	0.96-4.77	0.06
Unknown etiology					
Mild	2	1			
Moderate, severe, or fatal	1	2			
Unknown severity	2	1			
Total	5	4			
Total	119	98	1.22	0.93-1.60	0.15

* Severity was defined as follows: mild - impairment not affecting functioning; moderate - functional impairment; and severe - a major change in life style or dependency.

Table 3. Confirmed Deaths According to Treatment Group

CATEGORY OF DEATHS (9th ICD CODES)	ASPIRIN	PLACEBO	RELATIVE RISK	95% CONFIDENCE INTERVAL	P-VALUE
Total cardiovascular deaths†	81	83	0.96	0.60-1.54	0.87
Acute myocardial infarction (410)	10	28	0.31	0.14-0.68	0.004
Other ischemic heart disease (411-414)	24	25	0.97	0.60-1.55	0.89
Sudden death (798)	22	12	1.96	0.91-4.22	0.09
Stroke (430,431, 434,436)‡	10	7	1.44	0.54-3.88	0.47
Other cardiovascular (402,421, 424,425,428,429, 437,440,441)	15	11	1.38	0.62-3.05	0.43
Total noncardiovascular deaths	124§	133	0.93	0.72-1.20	0.59
Total deaths with confirmed cause	205	216	0.95	0.79-1.15	0.60
Total deaths¶	217	227	0.96	0.80-1.14	0.64
(person-years)	(54894.6)	(54864.2)			

† For this analysis, all fatal cardiovascular events are included, regardless of prior nonfatal event.

‡ This includes ischemic: 3 aspirin, 3 placebo; hemorrhagic: 7 aspirin, 2 placebo; unknown etiology: 0 aspirin, 2 placebo.

§ This includes the one death due to gastrointestinal hemorrhage

¶ Additional events that could not be confirmed due to unavailability of records included 23 deaths (12 in aspirin and 11 in placebo), of which 11 were suspected to be cardiovascular (7 in aspirin and 4 in placebo) and 12 noncardiovascular (5 in aspirin and 7 in placebo).

Table 4. Risk of Total Myocardial Infarction Associated with Aspirin Use, by Level of Coronary Risk Factors

	ASPIRIN		PLACEBO			P-VALUE (Trend in RR)
	MI/Total	%	MI/Total	%	RR	
Age (years)						
40-49	27/ 4527	0.6	24/ 4524	0.5	1.12	
50-59	51/ 3725	1.4	87/ 3725	2.3	0.58	
60-69	39/ 2045	1.9	84/ 2045	4.1	0.46	
70-84	22/ 740	3.0	44/ 740	6.0	0.49	0.02
Smoke Cigarettes						
Never	55/ 5431	1.0	96/ 5488	1.8	0.58	
Past	63/ 4373	1.4	105/ 4301	2.4	0.59	
Current	21/ 1213	1.7	37/ 1225	3.0	0.57	0.99
Diabetes Mellitus						
Yes	11/ 275	4.0	26/ 258	10.1	0.39	
No	128/10750	1.2	213/10763	2.0	0.60	0.22
Parental History of MI						
Yes	23/ 1420	1.6	39/ 1432	2.7	0.59	
No	112/ 9505	1.2	192/ 9481	2.0	0.58	0.97
Cholesterol level (mg/100 ml)						
≤ 159	2/ 382	0.5	9/ 406	2.2	0.23	
160-209	12/ 1587	0.8	37/ 1511	2.5	0.29	
210-259	26/ 1435	1.8	43/ 1444	3.0	0.61	
≥ 260	14/ 582	2.4	23/ 570	4.0	0.59	0.04
Diastolic blood pressure (mm Hg)						
≤ 69	2/ 583	0.3	9/ 562	1.6	0.21	
70-79	24/ 2999	0.8	40/ 3076	1.3	0.61	
80-89	71/ 5061	1.4	128/ 5083	2.5	0.55	
≥ 90	26/ 1037	2.5	43/ 970	4.4	0.56	0.88
Systolic blood pressure (mm Hg)						
≤ 109	1/ 330	0.3	4/ 296	1.4	0.22	
110-129	40/ 5072	0.8	75/ 5129	1.5	0.52	
130-149	63/ 3829	1.7	115/ 3861	3.0	0.55	
≥ 150	19/ 454	4.2	26/ 412	6.3	0.65	0.48

Table 4 (continued)

	ASPIRIN		PLACEBO			P-VALUE (Trend in RR)
	MI/Total	%	MI/Total	%	RR	
Alcohol use						
Daily	26/ 2718	1.0	55/ 2727	2.0	0.45	
Weekly	70/ 5419	1.3	112/ 5313	2.1	0.61	
Rarely	40/ 2802	1.4	65/ 2897	2.2	0.63	0.26
Vigorous exercise at least once/week						
Yes	91/ 7910	1.2	140/ 7861	1.8	0.65	
No	45/ 2997	1.5	92/ 3060	3.0	0.49	0.21
Body mass index (kg/m^2)						
$\leq$ 23.0126	26/ 2872	0.9	41/ 2807	1.5	0.61	
23.0127-24.4075	32/ 2700	1.2	46/ 2627	1.8	0.68	
24.4076-26.3865	32/ 2713	1.2	75/ 2823	2.7	0.44	
$\geq$ 26.3866	49/ 2750	1.8	76/ 2776	2.7	0.65	0.90

Table 5. Side Effects by Treatment Group

CATEGORY OF EVENTS (9th ICD CODES)	ASPIRIN N	ASPIRIN %	PLACEBO N	PLACEBO %	P-VALUE
Gastrointestinal symptoms (except ulcer)	3843	34.8	3779	34.2	0.48
GI discomfort (535)	2882	26.1	2823	25.6	0.45
Other non-infectious disorders of the digestive tract (536,537.8,537.9)	345	3.1	288	2.6	0.02
Miscellaneous symptoms of the digestive tract (533.123,787,789.0)	2384	21.6	2405	21.8	0.75
Upper GI ulcers	169	1.5	138	1.3	0.08
Esophageal ulcer (530.2)	11	0.1	6	0.05	0.23
Gastric ulcer (531)	25	0.2	15	0.1	0.11
Duodenal ulcer (532)	46	0.4	27	0.2	0.03
Peptic ulcer (533)	156	1.4	129	1.2	0.11
Gastrojejunal (534)	3	0.03	4	0.04	0.70
Bleeding problems	2979	27.0	2248	20.4	<0.0001
Easy bruising (459)	1587	14.4	1027	9.3	<0.0001
Hematemesis (578.0)	38	0.3	28	0.3	0.22
Melena (578.1)	364	3.3	246	2.2	<0.00001
Nonspecific GI bleeding (578.9)	440	4.0	422	3.8	0.55
Epistáxis (784.7)	862	7.8	640	5.8	<0.0001
Other bleeding* (599.7,958.2)	724	6.6	596	5.4	0.0004

*29% were related to shaving or brushing teeth (32% aspirin, 27% placebo), and 72% were hematuria (70% aspirin, 75% placebo)

Table 6. Direct and Indirect Comparisons Between Various Antiplatelet Therapies from the Overview of Results of 25 Randomized Trials (46) for the Combined Endpoint of Important Vascular Events

Direct Comparisons* (total events/patients)	Difference in favor of aspirin (% ± SD)
Aspirin vs. sulfinpyrazone (32,45,47)	
(54/346 vs. 74/357)	28 ± 17
Aspirin vs. aspirin + dipyridamole (17-18,30-31,36,48)	
(275/1597 vs. 279/1597)	2 ± 9

Indirect Comparisons**	Difference in favor of antiplatelet therapy (% ± SD)
Aspirin 0.9-1.5 grams daily vs. nil	23 ± 4
Aspirin 0.3 grams daily vs. nil	24 ± 8
Sulfinpyrazone vs. nil	17 ± 8
Aspirin + dipyridamole vs. nil	31 ± 5

* Reductions in risk of suffering an important vascular event (stroke/MI/vascular death), derived from separate overviews of the trials testing these two antiplatelet regimens against each other

** Reductions in risk of suffering an important vascular event, derived from comparing these four results from general overview of trials testing each specific agent vs. no treatment

Table 7. Suspected Evolving MI and Survivors of MI: Reductions in Risk (% ± SD) in Vascular Events Among Those Assigned Antiplatelet Therapy

Endpoint	Suspected Evolving MI (ISIS-2)	Survivors of MI (Antiplatelet Overview)
Nonfatal reinfarction	49 ± 9	31 ± 5
Nonfatal stroke	46 ± 17	42* ± 11
Total vascular death	23 ± 4	15 ± 5
Any vascular event	28 ± 4	25 ± 5

*The 42% reduction was observed in patients who had a history of MI.

A 27% reduction in risk was observed in patients who had any history of vascular disease (stroke, MI, TIA, etc.).

Table 1a. Aspirin in Primary Prevention (U.S. Physicians' Health Study and British Doctors' Trial Results)

	Reduction (% ± SD)		
Endpoint	U.S. Physicians' Health Study	British Doctors' Trial	Overview of both trials
Nonfatal MI	39 ± 9	3 ± 19	32 ± 8
Nonfatal stroke	*↑19 ± 15	↑13 ± 24	↑18 ± 13
Total cardiovascular death	2 ± 15	7 ± 14	5 ± 10
Any vascular event	18 ± 7	4 ± 12	13 ± 6

*↑ denotes a nonsignificant increase in stroke among aspirin-allocated subjects

TABLE 8

Patients for whom the Code has not been Revealed

1.	1101455	possible MI
2.	1109630	MI
3.	1185682	MI
4.	1243281	MI
5.	1247039	MI
6.	1446578	Disconfirmed
7.	1478222	
8.	1631745	Disconfirmed
9.	1665041	
10.	1729580	
11.	1840836	MI
12.	1868296	
13.	1888874	
14.	1977004	MI
15.	1993296	
16.	2101682	Dropout
17.	2605984	probable subendocardial MI
18.	3045443	Disconfirmed
19.	3182578	MI
20.	3533743	No Hospital Records
21.	3656904	No Hospital Records

TABLE 9
DEATHS FROM ACUTE MYOCARDIAL INFARCTION (AMI)

PLACEBO

	ID Age(years)	Symptoms and Specific Tests	Autopsy Findings	Reported Cause of Death	History	Comments
1.	1107432 54	Found dead	Severe atherosclerosis, recent coronary thrombosis	ASCHD		
2.	1319725 60	Collapse, V. fibrillation, PVCs, RBBB, Coma, CPK↑ , EKG+		Lobar pneumonia, anoxic encephalopathy	HT	Difibrillated, extensive acute ant. wall MI by EKG
3.	1414267 54	Crescendo angina V. ertopy, asystole CPK↑ ,EKG+	Large AMI, severe narrowing of all 3 coronaries, no thrombi	AMI, ASCVD		
4.	1525942 60	Pain, EKG+ CPK↑	AMI	Myocardial Rupture MI, ASCAD		
5.	1561313 61	Pain, EKG+ enzymes↑		Cardiogenic shock, acute pulm. embolism AMI		
6.	1927808 57	Found dead	Coronary atheroclerosis, thrombosis	ASHD	Diabetes Mel.	
7.	2116514 57	Pain, diaph. PVCs, V. Tach. V. Fibrillation EKG+		AMI	Heavy smoker, drinker	Cerebral bleed. in 1983
8.	2124796 55	Found dead	Thrombosis of rt. coronary artery	Occlusive coronary atherosclerosis		
9.	2239697 70	Pain, shortness of breath, syncope EKG+		AMI, CAD		
10.	2345919 50	Difficulty in breathing, felt bad, tachycardia, V. fibrillation, bypassed		AMI (during cath. CABG)	Nonspecific chest pain for 2 years before death	Previous MI in 1981
11.	2709793 61	CHF, VPCs, Sinus tach., EKG+		Acute Pulmonary edema, AMI, Cor. Atherosclerosis		Event occurred while water skiing

TABLE 9 (Cont.)
DEATHS FROM ACUTE MYOCARDIAL INFARCTION (AMI)

PLACEBO

	ID Age(years)	Symptoms and Specific Tests	Autopsy Findings	Reported Cause of Death	History	Comments
12.	2848734 68	Found dead	Acute anteroseptal, MI	ASHD		
13.	2905266 60	Severe chest pain, LDH ↑, EKG+		Massive MI, hypoxic encephalorathy, pneumonia		
14.	3083799 64	Sudden collapse, full arrest	Severe coronary atherosclerosis	Cardiac arrest, VF, ASCVD	HT	CPR no effect
15.	3199710 66	Coma	ASVD generalized, coronary thrombosis,	Cardiac arrest, MI, CHD	HT	Anoxic brain, bypassed. Died within 1 hr.
16.	3303296 61	Sudden severe pain, diaphoresis, palor EKG+, enzymes-		AMI, ASHD		Acute extensive anterolat. MI etc. by EKG
17.	3338008 66	Chest pain, CPK ↑ LBBB		CPA, AMI (possible)		Died within 16 hrs.
18.	3395737 62	Chest pain, hypotension, EKG+		AMI, cardiogenic shock	IHD	Old MI? CABG in 1976
19.	3433287 60	Chest pain, EKG changes		Cardiac arrest	HT, unstable angina	EKG questionable by hospital
20.	3645770 67	Sudden collapse, junctional rhythm	Thrombosis in LAD, Rupture of L. ventricle	AMI		CPR unsuccessful
21.	3726797	Indigestion, collapse, atrial fibril., EKG+		Cardiac arrest due to arrhythmia, AMI, anoxic encephalopathy	COPD, chronic bronchitis, HT	
22.	3900939 65	Severe chest pain, V. Fibril. EKG+, died during PTCA	No gross infarct, scattered foci of necrotic myocard. cells. (microscopically)	Acute coronary thrombosis, CAS	Progressive angina	Bypassed 9 years earlier, died within 1 hour

TABLE 9 (Cont.)
DEATHS FROM ACUTE MYOCARDIAL INFARCTION (AMI)

PLACEBO

	ID Age(years)	Symptoms and Specific Tests	Autopsy Findings	Reported Cause of Death	History	Comments
23.	3901040 76	Chest pain, HT, EKG+		MI, cardiac arrest	HT	Died within 2 hours difficult to read physician's notes
24.	4242965 79	Chest pain, hypotension, atrial fibr., LBBB, PVCs, V. tachy., diffuse pulmonary embol. (x-ray)		AMI	Arial. fibr.	Died within 5 hours
25.	4293574 82	Pain, SGOT↑, LDH↑, EKG+, incompl. RBBB		Cardiogenic shock, AMI		L. atrium enlargement
26.	4351409 82	Chest pain, nausea, lightheadedness, bloating, CPK↑, EKG+		AMI		
	1841300 77	Died from stroke (intracranial hemorrhage)				
	3151302	Died suddenly at home. No attending physician or autopsy.				

Abbreviations

ASCAD = atherosclerotic coronary artery disease
ASCHD = atherosclerotic heart disease
ASCVD = atherosclerotic vascular disease
CABG = coronary artery bypass grafting
CAD = coronary artery disease
CHD = coronary heart disease
CPA = cardiopulmonary arrest
HT = hypertension

TABLE 9 (Cont.)
DEATHS FROM ACUTE MYOCARDIAL INFARCTION (AMI)

ASPIRIN

	ID Age(years)	Symptoms and Specific Tests	Autopsy Findings	Reported Cause of Death	History	Comments
1.	1244567 85	Found dead	Thrombosis of rt. coronary artery	AMI, thrombosis of RCA, CASD		Found fallen down
2.	1416987	Record not seen				
3.	1787054 58	Symptoms, EKG+		Acute inferior, MI rt. coronary artery occlusion, ASHD		
4.	2300815 67		Thrombosis of rt. coronary artery	Ventr. arrhythmia, thrombosis rt. coron. artery.		Was hiking in Grand Canyon when he died
5.	2464543 71		Old scar (inf.) no gross evidence of infarct. Microscopic: very fresh subendocardial infarction	Ventricular fibrillation	Disecting aneurism 12 years ago	Died within 1 hour
6.	2505880 53	Chest pain, CPK↑, LDH↑, SGOT		AMI, cardiogenic shock, pulmonary edema		
7.	2643987 72	Symptoms, EKG+	Old MI	Respiratory insufficiency, pneumonia	Recurrent angina, arrhythmia, COPD	CABG 7/1/86 MI 7/13/86
8.	3333659 54	Found dead	Severe atherosclerosis of rh. coronary a. with hemorrhage in a plaque Microscopic: Early ischemic changes	Cardiac arrest, AMI, ASHD		
9.	3396970	Record not seen				
10.	3623251	Pain, EKG+	AMI	Cardiogenic shock, AMI, ASHD		

TABLE 10
SUDDEN DEATH

PLACEBO

	ID Age(years)	Symptoms and Specific Tests	Autopsy	Reported Cause of Death	History	Comments
1.	1521296 66			Arrhythmia due to MI	ASCHD	Wife said symptoms from day before, no sudden death
2.	1585043 49	Found unresponsive in bathtub	No cause of death found			Original records in study files lost
3.	1712930 66	Ventricular fibrillation,		AMI due to ASHD		Felt weak for a week before event, CPR
4.	1718019	Found dead on lawn				He was fertilizing the lawn when he dropped dead
5.	1740228 69	Bradycardia supraventricular rhythm, ventricular ectopy		Cardiopulmonary arrest	Pernicious anemia ASCHD,	LVH B-blockers
6.	2396415 74	Vertigo, ventr. arrhythmia, diplopia, tongue numbness, PVCs, interatrial block, long QT		ASCVD	HT, TIA, disoriented	Persantine Aspirin propranolol
7.	2630055 60	Collapsed, cyanotic		Cardiopulmonary arrest	COPD, asthma, collapsed lung CAD	Wife believes he had premonition of death, CPR no effect
8.	2887265 63	Found unconscious on the floor, groaning		Arrhythmia due to MI		
9.	3006817 67	Respiratory distress dead on arrival to EM		Cardiac arrest due to MI	ASCVD, bronchial asthma, COPD, TB	Died within 30 minutes
10.	3119950 57	Found dead in bed		Hypertensive CVD	CVD for 10 years, HT, hypercholesterolemia, heavy smoker, obese	Took pills faithfully every day, personality A clonidine, diuretics
11.	3289885 55	Found unconscious on floor, VF		AMI, VF		No one present
12.	3637150 66	Died suddenly		AMI (physician's assumption)	HT, chest pain Thiazide, tenormin	3 yrs before event hospital check up found no signs of active heart

TABLE 10 (Cont.)
SUDDEN DEATH

ASPIRIN

	ID Age(years)	Symptoms and Specific Tests	Autopsy	Reported Cause of Death	History	Comments
1.	1169359 76	Found dead		Ventr. Fibrillation	HT, overweight, smoker, disection of aorta 1981	Atenolol-HCTZ for HT
2.	1262270 51	Found dead with fractured lower incisors	Cerebral edema, lung edema, hyper-emia, no signs of ather-osclerosis, or heart D	Cardiac arrhythmia		He was alone in the desert target shooting
3.	1513825 58	Found dead on floor		Sudden MI	ASCHD for 2	Had been fishing, worked hard at home
4.	1542532 75	Died during sleep		Cardiac Arrest due to MI		
5.	1660318 69	Arrested during sleep		Cardiac arrest due to CAD		Arrived in hospital under CPR
6.	1679310 56	Died in garden working in warm weather		Extensive AMI, or electrolite imbalance		Died in about 2 hrs.
7.	1682315 59	Found dead		ASCVD		He took pills
8.	1712641	Found dead		MI	ASCVD	Was living alone
9.	1960760 49			Acute Cardio-respiratory failure, AMI	ASCHD	No other information except death certificate
10.	2285847 75	Found dead		Cardiopulmonary arrest	PVD, I. Claudic.	Daily aspirin
11.	2615053 53	Chest pain, cold feet, cardiac arrest, CPK↑		Cardiac arrest (CPR ∃ effect)	ASCVD	Unusually tired for a week, chest pain for 2 days, cold feet.
12.	2652327 54	Pain while playing racketball, collapse, vomit	Massive aspiration of gastric contents, moderate-severe 3 vessel atheroscl., extensive old	Cardiopulmonary arrest due to VF due to ASHD	HT	He was taking lopressor, lots of aspirin

TABLE 11

Some Old MIs, not Considered as Events

	Placebo	Aspirin	Assignment Not Revealed
1.	1704663	1446289	1101455
2.	2361939	1746780	1109630
3.	2609682	2122125	1185682
4.	2720670	2153129	1247039
5.	1933296**	2206343	1729580
6.	2824546	2548539	1840836
7.	2903702	2609530	1888874
8.	3094055	2622119	1977004
9.	3098010	1153928*	2101682
10.	3145681	3561753	2605984
11.	3217750	4238188	1243281
12.	3518886	4304706	1478222
13.	1294937	1187954*	1665041
14.			1863296

* These patients had two acute MIs which were confirmed but only one of them was included in the analysis.

** This patient had an acute and an old MI.

TABLE 12

Some Patients who had PTCAs

Placebo	Aspirin	Code Not Revealed
1. 1628564	1526576	1729580
2. 1666704	1828747	1109630
3. 1783395	3331965	1185682
4. 1855633	3629870	
5. 3042749		

Some Patients who had CABG

1. 1282513	1410047	1247039
2. 1291904	1405388	
3. 1341684	1446289	
4.	1451883	
5. 1434429	2153129	
6. 2750198	2208728	
7.	2678583	
8. 2903702	2881552	
9. 3133638	2987626	
10. 3457588	3561753	
11. 3771728	2853380	
12. 3073823		

Some Patients who had PTCA and CABG

3702993	1243281
	1631745
	3045443

Placebo patients # 1355921 and 2849544 had coronary bypasses before they entered the study.

Primary MI

M E M O R A N D U M

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

DATE: November 16, 1989

FROM: Director, Division of Gastrointestinal and Coagulation Drug Products, HFD-180

SUBJECT: Corrected Report on Aspirin for First Heart Attack dated November 13, 1989

TO: Director, Office of Drug Evaluation I, HFD-100

There were a few errors in the report which have been corrected in the attached copy.

Stephen Fredd, M.D.

cc:
IND: 17,275
HFD-180
HFD-180/ETriantas
KRobie-Suh
HFD-713/JHung/Tie-Hua Ng
HFD-181/CSO
HFD-180/SFredd
f/t deg: 11/8/89/11/13/89/11/16/89
w1040b

M E M O R A N D U M

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

DATE: NOV 13 1989

FROM: Director, Division of Gastrointestinal and Coagulation Drug Products, HFD-180

SUBJECT: Aspirin for the Prevention of First Heart Attack

TO: Director, Office of Drug Evaluation I, HFD-100

The use of aspirin to prevent an initial myocardial infarction is supported directly by data from the Physicians' Health Study, and not supported by the results of the British Doctors' Study. I will discuss these studies in reverse order.

Peto et al (BMJ, Vol. 296, Jan. 30, 1988, p 313-316) report the results of a six year randomized trial of 500 mg aspirin versus no aspirin in 5139 "apparently healthy male doctors." The question addressed by the trial was whether aspirin would reduce the incidence of and mortality from stroke, M.I., and/or other vascular conditions. Baseline characteristics of the two groups were reasonable well balanced as noted below.

TABLE I—*Baseline characteristics of study groups at entry. Except where stated otherwise figures are numbers (percentages) of doctors*

	Group allocated aspirin	Group allocated to avoid aspirin (controls)
No of participants	3429	1710
Age (years):		
<60	1604 (46·8)	804 (47·0)
60-69	1349 (39·3)	658 (38·5)
70-79	476 (13·9)	248 (14·5)
Smoking:		
Always non-smoker	859 (25·1)	395 (23·1)
Ex-smoker	1512 (44·1)	776 (45·4)
Current smoker, cigarettes only <20/day	224 (6·5)	123 (7·2)
Current smoker, cigarettes only ≥20/day	205 (6·0)	109 (6·4)
Other, or mixed, current smoker	625 (18·2)	307 (18·0)
Systolic blood pressure (mm Hg):		
<130	816 (23·8)	473 (27·7)
130-149	1235 (36·0)	584 (34·2)
>149	612 (17·8)	288 (16·8)
Not known	766 (22·3)	365 (21·3)
Mean (SE) pressure (mm Hg)	136·1 (0·29)*	135·1 (0·41)*
History of:		
Heart disease other than myocardial infarction	217 (6·3)	102 (6·0)
Angina	83 (2·4)	31 (1·8)
Transient ischaemic attack, etc†	92 (2·7)	44 (2·6)
Hypertension	349 (10·2)	159 (9·3)
Diabetes	69 (2·0)	32 (1·9)
Other vascular disease	111 (3·2)	76 (4·4)

*Difference ± 2 SE, p = 0·05; all other differences not conventionally significant.
†Any cerebrovascular disease other than stroke.

Compliance with the assigned regimen was not good. Halfway through the study roughly 30% of doctors allocated to take aspirin stopped doing so. In the no aspirin group "2% or so" of the subjects began to use aspirin per year. It is not clear from the report whether the events were in the compliant or non-compliant participants. The analyses are done on an intention-to-treat analysis. An evaluable subset analysis might have proven interesting. Nevertheless, the intention to treat results were as follows:

TABLE IV—*Rates of certain non-fatal vascular and non-vascular events by allocated treatment*

Non-fatal adverse events	First events/10 000 man years†	
	Group allocated aspirin (n=3429; subject years=18 220)	Controls (n=1710; subject years=9470)
Vascular and related conditions		
Non-fatal myocardial infarction:		
Confirmed myocardial infarction	42·5	43·3
Possible myocardial infarction	11·7	4·2
Non-fatal stroke:		
Confirmed stroke	32·4	28·5
(Disabling+other)	(19·1*+13·3)	(7·4*+21·1)
Probably haemorrhagic	1·6	2·1
Probably occlusive	6·9	4·2
Unknown aetiology	23·9	22·2
Possible stroke	3·2	3·2
Transient ischaemic attack:		
Confirmed transient ischaemic attack	15·9*	27·5*
Possible transient ischaemic attack	5·3*	14·8*
Blood, not cerebral	10·6	7·4
Other vascular conditions:		
Hypertension	227·9	216·5
Arrhythmias	140·8	137·3
Acute thrombotic event (pulmonary, venous, or other)	52·1	59·1
Other	96·7	100·3
Pepsic ulcer	46·8*	29·6*
Non-vascular events		
Non-fatal malignant neoplasm	63·2	61·2
Respiratory:		
Acute infections	149·3	162·6
Chronic bronchitis, emphysema	27·6	30·6
Asthma	33·5	42·2
Cataract	86·1	77·1
Migraine	197·1***	276·7***
Musculoskeletal disorders for which medical advice sought	544·1***	639·9***

Note: Non-fatal occurrences of a particular disease exclude occurrences in patients who later died of that disease.
*2p<0·05; **2p<0·01; ***2p<0·001.
†Estimated (without use of life table methods) as number of subjects ever affected divided by 1·882 or 0·947.

TABLE III—*Cause specific death rates by allocated treatment*

Underlying cause of death (and ICD category (9th revision))	Deaths/10 000 man years‡	
	Group allocated aspirin (n=3429; subject years=18 220)	Controls (n=1710; subject years=9470)
Definite myocardial infarction or stroke	63·2	62·3
410–414 Myocardial infarction	47·3	49·6
430–432 Haemorrhagic stroke	5·3	4·2
433–434 Occlusive stroke	4·3	3·2
Rest 430–439 Stroke, unknown aetiology	6·4	5·3
Other vascular and related causes	15·4	21·2
394–397 Rheumatic endocardial	1·6	0
Rest 390–399 Other rheumatic disease	0	0
400–409 Hypertensive disease	1·1	2·1
415 Pulmonary embolus	2·1	0
416 Respiratory heart disease	0·5	1·1
421, 424 Non-rheumatic endocardial	1·1*	5·3*
Rest 417–429 Other heart disease	3·2	3·2
441 Aortic aneurysm	2·1	4·2
Rest 440–459 Other vascular	1·1	1·1
530–535:		
Gastric haemorrhage	0·5	0
Pepsic ulcer (haemorrhagic)	0	3·2
Pepsic ulcer (perforated)	1·1	0
797–799 Unknown‡	1·1	1·1
Remaining (non-vascular) causes	64·8	76·0
150–152 Cancer of upper digestive tract	5·8	5·3
162 Cancer of lung	7·4	11·6
Rest 140–239 other neoplasms	26·6	31·7
460–489 Acute respiratory disease	4·3*	11·6*
490–519 Chronic respiratory disease	4·3	4·2
All other diseases	9·0	6·3
External causes (accidents, etc)	7·4	5·3
Total (all causes)	143·5	159·5

*2p<0·05.
†Estimated as number of deaths divided by 1·882 or 0·947.
‡Deaths from unknown causes all occurred abroad; anecdotal evidence suggests that all were vascular.

Ascertainment of these endpoints was by questionaire, correspondence, and medical records. The numbers in the tables are not events, but first events per 10,000 man years. A more clinically interpretable presentation of this data (and that of the U.S. Physicians' Health Study) is provided as follows:

British Doctors' Study

	ASA #(cases per 1000)	No ASA # (cases per 1000)
Non-Fatal M.I.s Confirmed	80 (23.5)	41 (24)
Possible	22 (6.5)	4 (2.4)
Total	102 (30)	45 (26.4)

Physicians' Health Study

	ASA #(cases per 1000)	Placebo # (cases per 1000)
Non-Fatal M.I.s	129 (11.7)	213 (19.4)

There were more non-fatal M.I. events per 1000 participants in the British study than in the U.S. study.

Yet the British study did not provide evidence that ASA prevented non-fatal M.I.s. If ASA is effective in preventing first heart attack, it is not clear why the study failed to show some trend or numerical superiority for ASA preventing non-fatal M.I.s. In the study aspirin administration significantly reduced migraine attacks, musculoskeletal pain, and the frequency of confirmed TIAs. Aspirin use between the two groups was sufficient to demonstrate these pharmacologic effects, so why did such effect not become manifest for non-fatal M.I.? It is noted that the confidence intervals were wide (-27% to & 24% M.I.s in either group). Sandercock (BMJ Volume 298, Jan. 14, 1989, p. 119) states that the confidence intervals for the reduction in odds of non-fatal M.I. in the British Study was 3% (95% confidence interval 62% reduction to 238% increase) while the U.S. study result was 43% (95% confidence interval 26% reduction to 55% reduction) so that "there is no significant difference in the magnitude or direction of the effect of treatment in either of these trials," but if possible non-fatal M.I.s are included, rather than a 3% decrease in favor of ASA, as reported by Sandercock, there is a slight increase in non-fatal M.I.s for those on ASA. The direction of the effect is then opposite to that of the Physicians' Health Study. It would be interesting to have the raw data to review, but in its absence the null result of this trial remains disturbing.

From a safety viewpoint, the expected gastrotoxic effects of ASA were noted, and disabling stroke was significantly more frequent in the ASA group (although the frequency of TIAs was reduced in the ASA group). One would not on the basis of this trial recommend the use of aspirin to prevent an initial heart attack, and I do not believe one can dismiss the study as uninterpretable, since for some parameters it provided pharmacologically reasonable results.

The antiplatelet trialist collaboration (BMJ, Jan. 30, 1988, 296, 320-331) provides a meta analysis of 31 randomized trials of antiplatelet drugs for the prevention of vascular disease. The following results are provided in the article:

TABLE IV—*Non-fatal myocardial infarctions recorded in trials of antiplatelet treatment (numbers affected but with survival to end of study)*

	Basic data		Statistical calculations (treatment group only)	
	Allocated antiplatelet treatment	Allocated to control group	Observed No minus expected (O−E)	Variance of O−E
Completed cerebrovascular trials:				
ESPS	21/1250	35/1250	−7·0	13·7
UK-TIA	42/1621	34/814	−8·6	16·4
AICLA	4/400	9/204	−4·6	2·8
CCSG	15/446	0/139	3·6	2·7
Swedish stroke	10/253	10/252	0	4·8
McMaster	4/222	4/225	0	2·0
Toulouse	0/284	2/156	−1·3	0·5
AITIA	4/153	2/150	1·0	1·5
Toronto	?/143	?/147	—	—
DCS	2/101	8/102	−3·0	2·4
Stoke	?/85	?/84	—	—
Tennessee	?/73	?/75	—	—
German TIA	0/30	0/30	0	0
All cerebrovascular trials (excluding six still in progress (table II))	≥206/8689 (2%)*		−19·9 (2·9 SD from zero; 1p=0·002)	46·7 Typical odds reduction 35% (SD 12%)
Myocardial infarction trials:				
AMIS	175/2267	214/2257	−19·9	88·9
PARIS-II	71/1563	111/1565	−19·9	42·9
PARIS-I	120/1620	40/406	−7·9	23·6
Cardiff-II	31/832	63/850	−15·5	22·2
ART	43/306	50/814	−3·3	21·9
CDP-A	28/758	32/771	−1·7	14·4
GDR	32/672	60/668	−14·1	21·4
Cardiff-I	12/615	15/624	−1·4	6·6
ARIS	15/365	33/362	−9·1	11·2
GAMIS	11/317	16/309	−2·7	4·5
All myocardial infarction trials	1172/18 441 (6%)*		−95·6 (6·0 SD from zero; 1p<0·0001)	257·7 Typical odds reduction 31% (SD 5%)
Unstable angina trials:				
VA (main + pilot)	27/687	50/701	−11·1	18·2
McMaster (three groups v one)	24/416	7/139	0·8	5·5
All unstable angina trials	108/1943 (6%)*		−10·4 (2·1 SD from zero; 1p=0·02)	23·7 Typical odds reduction 35% (SD 17%)
All available trials	>1486/27 073 (5%)*		−125·9 (7·0 SD from zero; 2p<0·0001)	322·1 Typical odds reduction 32% (SD 5%)

*Totals for treated and control groups combined (as separate totals could not validly be compared).

In the myocardial infarction trials, each study showed a reduction in new infarctions observed versus those expected. Some heterogeneity appeared in the cerebrovascular trials, but there is, even in this group of studies, a preponderance of results favoring ASA. The results supporting approval of aspirin for the prevention of second myocardial infarction were from numerous trials, and consistently supported that indication. What we have for support of the first heart attack indication for ASA is one possibly positive study and one null result. The possibly positive study is, of course, the U.S. Physicians' Health Study.

The U.S. Physicians' Health Study (NEJM, 321: 129-135 (July 20), 1989) is a randomized, double blind placebo controlled factorial study of ASA (325 mg every other day) and beta carotene to determine if the ASA in "healthy" participants decreased cardiovascular mortality, and whether beta carotene reduced the incidence of cancer (this portion of the study is still ongoing). 261, 248 questionaires were mailed to U.S. male physicians, age 40-84 years of age; 112, 528 responses were received; 59, 285 were willing to participate of whom 33, 223 enrolled in an 18 week run-in period in which all took ASA and beta carotene. After the run-in those willing to continue participation were randomized in a factorial design to ASA, beta carotene, and placebo. The primary ASA endpoint was reduction in cardiovascular mortality, with secondary endpoints of reduction in M.I., stroke, TIAs and angina. The assessment was done by correspondence including questionaires and medical records where needed. There was an endpoints committee that made the final judgment as to whether an M.I. or stroke was to be counted as such, and a data monitoring board that on December 18, 1987 recommended early termination of the ASA component of the study because of the improbability of detecting a reduction in cardiovascular mortality until after the year 2000, and an extreme benefit noted for ASA in reducing the probability of having an M.I. The p value for early stopping had to be less than 0.0027. It must be emphasized since the interim analysis stopping p value had to be 0.0027, the trial might have continued for values greater than that value. For purposes of this discussion, p value results < 0.0027 will be considered statistically significant for efficacy.

Table 1. Confirmed Cardiovascular End Points in the Aspirin Component of the Physicians' Health Study, According to Treatment Group.*

End Point	Aspirin Group	Placebo Group	Relative Risk	95% Confidence Interval	P Value
Myocardial infarction					
Fatal	10	26	0.34	0.15–0.75	0.007
Nonfatal	129	213	0.59	0.47–0.74	<0.00001
Total	139	239	0.56	0.45–0.70	<0.00001
Person-years of observation	54,560.0	54,355.7	—	—	—
Stroke					
Fatal	9	6	1.51	0.54–4.28	0.43
Nonfatal	110	92	1.20	0.91–1.59	0.20
Total	119	98	1.22	0.93–1.60	0.15
Person-years of observation	54,650.3	54,635.8	—	—	—

*Additional events that could not be confirmed because records were not available included 17 myocardial infarctions (10 in the aspirin group and 7 in the placebo group) and 11 strokes (3 aspirin and 8 placebo).

In this analysis the p value for reduction in first M.I. (total and non-fatal) would be considered significant.

Subset analysis of M.I. by risk factors is provided as follows:

Table 4. Risk of Total Myocardial Infarction Associated with Aspirin Use, According to Level of Coronary Risk Factors.

	Aspirin Group	Placebo Group	Relative Risk	P Value of Trend in Relative Risk
	no. of myocardial infarctions/total no. (%)			
Age (yr)				
40–49	27/4527 (0.6)	24/4524 (0.5)	1.12	
50–59	51/3725 (1.4)	87/3725 (2.3)	0.58	0.02
60–69	39/2045 (1.9)	84/2045 (4.1)	0.46	
70–84	22/740 (3.0)	44/740 (6.0)	0.49	
Cigarette smoking				
Never	55/5431 (1.0)	96/5488 (1.8)	0.58	
Past	63/4373 (1.4)	105/4301 (2.4)	0.59	0.99
Current	21/1213 (1.7)	37/1225 (3.0)	0.57	
Diabetes mellitus				
Yes	11/275 (4.0)	26/258 (10.1)	0.39	0.22
No	128/10,750 (1.2)	213/10,763 (2.0)	0.60	
Parental history of myocardial infarction				
Yes	23/1420 (1.6)	39/1432 (2.7)	0.59	0.97
No	112/9505 (1.2)	192/9481 (2.0)	0.58	
Cholesterol level (mg per 100 ml)*				
<159	2/382 (0.5)	9/406 (2.2)	0.23	
160–209	12/1587 (0.8)	37/1511 (2.5)	0.29	0.04
210–259	26/1435 (1.8)	43/1444 (3.0)	0.61	
≥260	14/582 (2.4)	23/570 (4.0)	0.59	
Diastolic blood pressure (mm Hg)				
≤69	2/583 (0.3)	9/562 (1.6)	0.21	
70–79	24/2999 (0.8)	40/3076 (1.3)	0.61	0.88
80–89	71/5061 (1.4)	128/5083 (2.5)	0.55	
≥90	26/1037 (2.5)	43/970 (4.4)	0.56	
Systolic blood pressure (mm Hg)				
<109	1/330 (0.3)	4/296 (1.4)	0.22	
110–129	40/5072 (0.8)	75/5129 (1.5)	0.52	0.48
130–149	63/3829 (1.7)	115/3861 (3.0)	0.55	
≥150	19/454 (4.2)	26/412 (6.3)	0.65	
Alcohol use				
Daily	26/2718 (1.0)	55/2727 (2.0)	0.45	
Weekly	70/5419 (1.3)	112/5313 (2.1)	0.61	0.26
Rarely	40/2802 (1.4)	65/2897 (2.2)	0.63	
Vigorous exercise at least once a week				
Yes	91/7910 (1.2)	140/7861 (1.8)	0.65	0.21
No	45/2997 (1.5)	92/3060 (3.0)	0.49	
Body-mass index†				
≤23.0126	26/2872 (0.9)	41/2807 (1.5)	0.61	
23.0127–24.4075	32/2700 (1.2)	46/2627 (1.8)	0.68	0.90
24.4076–26.3865	32/2713 (1.2)	75/2823 (2.7)	0.44	
≥26.3866	49/2750 (1.8)	76/2776 (2.7)	0.65	

*To convert cholesterol value to millimoles per liter, multiply by 0.02586.

†Body-mass index is the weight (in kilograms) times the height (in meters) squared.

Other than no apparent difference in males below 50 years of age, and the suggestion of increased protection in participants with lower levels of cholesterol, the purported benefit of ASA to prevent first heart attack seems to be present in all strata.

The benefit in preventing first M.I. (total) is due to the difference in non-fatal M.I., although it has been suggested that ASA provided a significant benefit in reducing fatal M.I.s. We do not concur with that suggestion because 1) the result does not meet the specified stopping p value, and 2) when the fatal M.I. and sudden death results are summed there is no significant difference between the ASA and placebo groups (32 ASA versus 38 placebo).

If non-fatal M.I. and non-fatal stroke events are compared in the two groups by removing cardiovascular deaths from the sum of non-fatal M.I., non-fatal stroke and cardiovascular death, the result is no longer significant for early trial termination.

	ASA # of cases	Placebo # of cases	p*
Non-fatal M.I. + Non-fatal stroke	226 11037	287 11034	0.018

*two sample T test

Evidence of some other expected pharmacologic benefit of ASA in the Physicians' Health Study to internally support the reported benefit on first M.I.s would be useful. According to protocol TIAs and angina results were to be provided. Neither is reported in the published reports, but we requested reports of the results for TIA, DVT and pulmonary embolism for the two cohorts. No report of the angina group is available.

For TIA the results are as follows:

Incidence of TIA
Confirmed by the Endpoints Committee
During the Randomized Period for
Four Treatment Groups
by Five-Year Age Groups

Treatment Group

Age Group	Aspirin	Placebo	RR	P	95% CI
40-44	0	1			
45-49	1	6			
50-54	4	8	0.3326	0.0257	(0.138, 0.799)
55-59	12	10	1.1912	0.6825	(0.516, 2.748)
60-64	7	16	0.4275	0.0577	(0.189, 0.968)
65-69	9	6	1.5985	0.4306	(0.581, 4.398)
70-75	8	9	0.8944	0.8188	(0.346, 2.314)
76-79	2	2			
80-84	1	1	1.0162	0.9843	(0.205, 5.036)

For DVT the results are as follows:

Incidence of DVT
Confirmed by the Endpoints Committee
During the Randomized Period for
Four Treatment Groups
by Five-Year Age Groups

Treatment Group

Age Group	Aspirin	Placebo	RR	P	95% CI
40-44	2	4	0.4795	0.4124	(0.097, 2.376)
45-49	10	6	1.7347	0.3159	(0.651, 4.622)
50-54	7	6	1.1980	0.7716	(0.404, 3.553)
55-59	8	8	0.9976	0.9887	(0.374, 2.658)
60-64	6	8	0.7397	0.5805	(0.259, 2.109)
65-69	4	5	0.8007	0.7423	(0.217, 2.958)
70-75	8	5			
76-79	0	1			
80-84	0	1	1.1511	0.7867	(0.418, 3.167)

For PE the results are as follows:

Incidence of Pulmonary Embolism
Confirmed by the Endpoints Committee
During the Randomized Period for
Four Treatment Groups
by Five-Year Age Groups

Treatment Group

Age Group	Aspirin	Placebo	RR	P	95% CI
40-44	1	2			
45-49	5	3	1.2416	0.7631	(0.381, 4.048)
50-54	3	3			
55-59	3	3	0.9959	0.9974	(0.321, 3.088)
60-64	5	4			
65-69	3	2	1.3394	0.5993	(0.470, 3.819)
70-75	6	5			
76-79	1	1			
80-84	0	1	1.0111	0.9912	(0.355, 2.883)

For TIA there are numerically fewer cases in the ASA group, but this is not significant and is not consistent over various age groupings. The extreme result in reduction of first M.I.s is not supported by any of the above findings.

Although the result in non-fatal M.I. appears positive, there is another unresolved issue that raises some doubt about the result; that is the extent of prior M.I. in the study population. Given that we know ASA (300-325 mg daily) reduces the probability of a second heart attack (typical odds reduction 31% with a 5% standard deviation according to the antiplatelet trialist article page 326), even if individuals with prior M.I. were evenly distributed in the two groups, a beneficial effect would only be present in the ASA treated group. What is currently viewed as a benefit to prevent first heart attack may actually have been due to prevention of second heart attack, at least in terms of statistical significance.

Dr. Triantas noted the fact that "at least 40 of the 512 (8%) patients" who reported a non-fatal M.I. has evidence of an old infarct. Also, "at least 38 of these 512 (7%) had PTCAs (12) or CABGs (22) or both (4)." She did not evaluate the 22071 participant database, and we do not know the extent of previous M.I. within the total study population. However, if one makes some assumptions, the possible impact of this finding on the first heart attack result becomes clear.

Using assumptions that 8% of study population had a prior M.I., that there was a 2% per year secondary M.I. rate (from Cardiff-I) and a 31% or 41% odds reduction benefit of ASA to prevent second heart attack (from antiplatelet trialist paper, ibid), Drs. Hung and Ng of Biometrics have provided the following analyses.

"Table 5
Bias due to the Inclusion of Participants with prior MIs

				MI Incidence			
Treatment Group	Prior MI	n	%	Expected[1]	Expected[2]	Expected[3]	Observed
Aspirin	No	10,154	(92%)	---	99.5	105	NA
	Yes	883	(8%)	---	73	62	NA
	Total	11,037	(100%)	189	173	167	139
Placebo	No	10,151	(92%)	---	99.5	105	NA
	Yes	883	(8%)	---	106	106	NA
	Total	11,034	(100%)	189	205	211	239

[1]Under the null hypothesis that aspirin has no effect on first MI, and no adjustment is made for inclusion of participants with MIs prior to randomization.

[2]Under the null hypothesis that aspirin has no effect on first MI, and the assumptions that the placebo recurrence rate is 12% and the reduction of recurrence rate due to aspirin is 31%.

[3]Under the null hypothesis that aspirin has no effect on first MI, and the assumptions that the placebo recurrence rate is 12% and the reduction of recurrence rate due to aspirin is 41%.

Table 6
Treatment Comparison Based on Estimated
Observed Number of Primary MIs

Reduction of Recurrence Rate Due to Aspirin	Treatment Group	n	Estimated Observed Number of Primary MI[1]	(%)	P-value[2]
31%	Aspirin	10,154	66	(0.65)	0.00054
	Placebo	10,151	133	(1.31)	
41%	Aspirin	10,154	76	(0.75)	0.0036
	Placebo	10,151	133	(1.31)	

[1]Estimated observed number of primary MIs
= Observed MIs - Expected number of secondary MIs.
The MI recurrence rate of the placebo group is 12%.

[2]Two sided-test for equality of two proportions using normal approximation.
Note: the variability of estimating the observed number of primary MIs has been taken into account by this test."

The p value using a 41% recurrence rate reduction for second heart attack is no longer significant.

Although we suggested that Dr. Hennekens identify those participants with prior M.I.s, remove them from the analysis, and provide what would be an "evaluable" analysis (since patients with prior M.I.s were not by protocol eligible for the study) Dr. Hennekens suggested instead in his response of 9/25/89 that "primary prevention, to me, means prevention of the clinical manifestations of coronary artery disease such as diagnosable and diagnosed acute myocardial infarction." He goes on to state that no available test would provide a "gold standard for the presence or absence of acute myocardial infarction," and the population screened was at very low risk, so that tests applied would likely give false positives. Finally, Dr. Hennekens states that the participants were "apparently healthy," and this would be the status of the general population for whom ASA would be considered.

Clearly, there are tests for coronary artery disease, and participants with pre-existing M.I. can be and have been identified within the study cohort. As simple a screening procedure as an EKG might have been useful, and surely we do not want "apparently healthy" people self-medicating themselves without a physician's advice based on a clinical evaluation. It is true that, were a benefit of ASA to prevent first heart attack demonstrated, it would be unimportant to know whether a primary or secondary effect was operating in any individual patient. However, this trial was meant to determine whether or not a primary benefit existed, and it is therefore important to be sure that the results are due to primary rather than secondary protection for purposes of drug approval of the first heart attack claim.

The foregoing analysis does not prove that the result in first M.I. is not significant. It does suggest that we could be mistaken in accepting the result of the Physicians' Health Study as the sole basis for approval.

If one does conclude that this study does support a role for ASA in prevention of first heart attack, can we conclude as Dr. Hennekens does that the participants are typical of asymptomatic healthy people in whom the drug should be used?

To address this question we would note that the subjects in the Physicians' Health Study were unusual in their health profile. It was expected that 733 cardiovascular deaths would occur during the trial; 164 occurred. 421 deaths (all causes) occurred, a 2% overall death rate. Of the 378 M.I.s noted in the trial, 36 (10%) were fatal. Contrasting these findings with those of the British Doctors' Study, there was an 8% overall death rate, and a 48% M.I. death rate. One can surmise that the populations were different in health status. The demographics of the populations involved support the suggestion that the U.S. participants were much healthier than average, and different in important ways from the British participants.

U.S.

	Aspirin N = 11,034	Placebo N = 11,037
Age (years)	53.2 ± 9.5	53.2 ± 9.5
History of hypertension (%)	13.5	13.6
Systolic BP (mmHg)	126.1 ± 11.3	126.1 ± 11.1
Diastolic BP (mmHg)	78.8 ± 7.4	78.8 ± 7.4
History of high cholesterol (%)	17.5	17.3
Cholesterol level (mg)	212.1 ± 44.2	212.0 ± 45.1
History of diabetes (%)	2.3	2.2
History of angina (%)	1.3	1.2
Parental MI (%)	13.0	13.1
Current smoking (%)	11.0	11.1
Past smoking (%)	39.4	39.1
Daily alcohol (%)	24.9	25.0
Exercise > 1/month (%)	10.0 ± 8.4	10.0 ± 8.6
Body mass index (kg/m^2)	24.9 ± 3.1	24.9 ± 3.0
Multivitamin use (%)	19.9	19.9

British

TABLE 1—*Baseline characteristics of study groups at entry. Except where stated otherwise figures are numbers (percentages) of doctors*

	Group allocated aspirin	Group allocated to avoid aspirin (controls)
No of participants	3429	1710
Age (years):		
<60	1604 (46·8)	804 (47·0)
60-69	1349 (39·3)	658 (38·5)
70-79	476 (13·9)	248 (14·5)
Smoking:		
Always non-smoker	859 (25·1)	395 (23·1)
Ex-smoker	1512 (44·1)	776 (45·4)
Current smoker, cigarettes only: <20/day	224 (6·5)	123 (7·2)
Current smoker, cigarettes only: ≥20/day	205 (6·0)	109 (6·4)
Other, or mixed, current smoker	625 (18·2)	307 (18·0)
Systolic blood pressure (mm Hg):		
<130	816 (23·8)	473 (27·7)
130-149	1235 (36·0)	584 (34·2)
>149	612 (17·8)	288 (16·8)
Not known	766 (22·3)	365 (21·3)
Mean (SE) pressure (mm Hg)	136·1 (0·29)*	135·1 (0·41)*
History of:		
Heart disease other than myocardial infarction	217 (6·3)	102 (6·0)
Angina	83 (2·4)	31 (1·8)
Transient ischaemic attack, etc†	92 (2·7)	44 (2·6)
Hypertension	349 (10·2)	159 (9·3)
Diabetes	69 (2·0)	32 (1·9)
Other vascular disease	111 (3·2)	76 (4·4)

*Difference=2 SE, p=0·05; all other differences not conventionally significant.
†Any cerebrovascular disease other than stroke.

From the baseline characteristics reported in the two studies, the U.S. study participants were younger, fewer smoked, systolic pressure was lower and they had less angina than those in the British study. A majority of those in the U.S. study exercised vigorously at least once a week (15771/22071, 72%).

Because of the clinical differences in the U.S. and British study populations, I would not favor pooling the results. The result on non-fatal M.I. in the U.S. study, if indeed true, occurred in a healthier than usual population. The non-replication in an older, more average population may be meaningful in ways not yet recognized. One might speculate that if there is a protective effect against non-fatal first myocardial infarction, it may be present only when the individual's coronaries or platelets have been "conditioned" by exercise or other factors to produce less of some negative factor such as endothelin or more of some positive agent such as TPA, or both. Under these adjunctive conditions, ASA may be protective (U.S. study). Without them, it may not be (British study). This theory may not be immediately appealing in that ASA is clearly useful in advanced vascular disease e.g. after a first heart attack, but it is likely that such patients are told to lose weight, adjust their diets, lower cholesterol, control blood pressure, exercise, and there may be other interventions. Adjunctive factors may well exist in settings where ASA's antiplatelet effect has proven useful. In "normal" subjects reduction of these risk factors with "conditioning" of the coronary vessels may be essential for efficacy. Although it is tempting to use the Physicians' Health Study as a pharmacologic demonstration that ASA prevents first heart attack, and then extrapolate that effect to "high risk" groups in order to justify the toxicity of long term ASA treatment, there is no direct data supporting the extrapolation. The experimental evidence that does exist, the British Doctors' Study, does not provide support. If the Physicians' Health Study result pertains only to those who have reduced risk factors, we would be in error to approve or label the drug for a population where risk factors have not been reduced. Replication of the Physicians' Health Study is needed, and replication is possible. A similar study, the Nurses' Health Study, has been proposed by Dr. Hennekens.

To the list of reasons supporting the proposal for replication of the U.S. study is the toxicity of ASA. NSAIDs in general and aspirin in particular have been associated with gastrointestinal side effects, such as bleeding. Endoscopic findings, such as ulcers, are of concern (see Graham and Smith, Ann. Int. Med 1986:104:390-398 and Am. J. of Gastroenterology 1988: 83 No. 10:1081-1084). Although using an ASA dose of 325 mg every other day would lessen the chances for toxicity, it would not eliminate the risks. The Physicians' Health Study utilized a run-in phase after which 11152 were excluded from randomization for side effects, poor compliance and unwillingness to participate. Given the run-in phase, it is not surprising that there was a non-significant between group difference in gastrointestinal discomfort (26.1% ASA versus 25.6% placebo), but 169 ASA participants versus 138 placebo ($p = 0.08$) developed ulcer of whom 38 ASA versus 22 placebo "experienced hemorrhage" ($p = 0.04$). 1 death from gastrointestinal hemorrhage in the ASA group was reported. Bleeding phenomena (easy bruising, hemotemesis, melena, epistaxis) was noted in 2979 ASA and 2248 placebo participants (p 0.00001).

Cerebral hemorrhage as a cause of stroke was more frequent in the ASA group (23 cases versus 12, p=0.06), which finding is also suggested by the statistically significant increase in disabling strokes of the British Doctors' Study.

Even though the subjects in the Physicians' Health Study were "selected" by a run-in phase, the expected toxicities of aspirin are suggested by the results, and in general use one might expect based on these findings that a third will drop out of a prophylactic regimen, an excess of ulcers G.I. bleeding, and hemorrhagic stroke will occur. The offset of these toxicities against the benefit in reducing non-fatal M.I.s must be weighed in making a final recommendation.

The Cardiovascular and Renal Advisory Committee on October 6, 1989 considered the data relevant to ASA for the prevention of first heart attack, specifically the Physicians' Health Study and the British Doctors' Study. Only the Physicians' Health Study was presented in detail. The majority voted for approval "based on this trial, for some claim in some group "(6 for, 3 against). Dr. Brater had suggested "high risk groups," and that he wanted "to avoid anything in the labeling that should indicate that it would go to healthy people." Dr. Packer suggested that the claim be for "prevention of non-fatal myocardial infarction in men over the age of 50 with coronary artery disease." Dr. Hennekens from the floor suggested "in men over 50 whose risk of first heart attack is sufficiently high to warrant the adverse effects of the drug." No final labeling recommendation was made, but, for the majority who voted for approval, it was clear that "for all men over 50" was unacceptable, whereas some wording indicating a population where the benefit would be worth the risk might be. The majority recommended that hypertension not be an exclusion, that prevention of first heart attack be a separate claim, and that the ASA dose be 325 mg every other day.

The minority, 1 to 3 members of the committee, were most concerned about the toxicity of ASA, and the number of normals who would be treated long term who would never develop a heart attack. The difficulty of clearly defining in labeling a subgroup for whom the drug might have a better risk-benefit ratio was also of concern. The minority did not dissent from the view that the result of the Physicians' Health Study was compelling evidence that ASA reduced the probability of a first heart attack, but may have placed greater emphasis on the British Doctors' Study and the combined safety profile of the drug than the majority in coming to a decision that ASA was not approvable for the prevention of first heart attack.

The Division has considered all available data, and recommends that ASA not be approved for the prevention of first heart attack until an additional study confirms the result from the Physicians' Health Study. One such study is planned by Dr. Hennekens' group and is awaiting funding. The reasoning for this recommendation is as follows:

1. The result of the Physicians' Health Study in non-fatal M.I.s is an isolated positive finding which when combined with non-fatal strokes becomes non-significant. These are still unresolved questions about the incidence of prior coronary artery disease in the total study population, and how that might effect any conclusion that ASA is effective for the prevention of first heart attack.

2. The null result of the British Doctors' Study cannot be dismissed, and gives no support to the contention that ASA works to prevent first heart attack in high risk subjects or others.

3. The toxicity of long-term ASA administration even at 325 mg every other day is not inconsiderable. The Physicians' Health Study prescreened participants for ASA intolerance, and does not provide a comprehensive safety profile of the drug for prophylaxis in all men over 50 or in high risk groups where toxicity may be greater and effectiveness has not been demonstrated.

4. Our usual requirement for approval of a new claim is for at least two positive studies. Since normal individuals would run risks in taking long-term ASA, we should be sure that there is a benefit and have a reasonable safety database that pertains to general use.

5. If the drug is demonstrated to work in normal individuals without multiple risk factors, we must consider labeling that includes that group. Exclusion of the normal risk group and inclusion only of high-risk patients (e.g. those with multiple uncorrected risk factors) might incorrectly focus on those for whom there is no data in support of the claim, while not providing for use in those for whom there is data. The labeling questions would be more reasonably resolved after evaluation of an additional study.

If you concur with the Division's recommendation, we would suggest that a letter to Dr. Hennekens under your signature be issued that, while we consider the result of the Physicians' Health Study some positive support for the use of ASA to prevent first heart attack, our usual standard is to require replication before approval of such a claim, and we would strongly recommend that such a replicative study be done.

We could provide this analysis to the Cardiovascular and Renal Disease Advisory Committee for their comment, the Antiplatelet Trialists at their meeting in March 1990, as a talk paper to the New England Journal of Medicine for professional comment, and/or in the Federal Register if you wish. I believe further consideration of this issue is essential before the agency acts on this claim.

We would be glad to meet with you to discuss the issues further.

Stephen Fredd M.D.

Stephen Fredd, M.D.

cc:
IND 17-275
HFD-180
HFD-180/ETriantas
KRobie-Suh
HFD-713/JHung/Tie-Hua Ng
HFD-181/CSO
HFD-180/SFredd
f/t deg: 11/8/89/11/13/89
wl040b

ASPIRIN IN THE PREVENTION OF STROKE

A. Prevention of Secondary Stroke:

1. "AICLA" Controlled Trial of Aspirin and Dipyridamole in the Secondary Prevention of Atherothrombotic Cerebral Ischemia. Stroke 14: 5, 1983) from the Clinique des Maladies du Systeme Nerveux, Hospital de la Salpetriere, Paris, France.

Eligibility: Patients who had experienced at least one cerebral or retinal atherothrombotic ischemic event, whether transient or completed during the preceding year, were eligible to enter the study. Isolated symptoms such as loss of consciousness, diplopia, vertigo, or loss of memory were not acceptable.

Exclusions:

Women under 50 years of age.

Comorbid conditions which could explain the symptoms (atrial fibrillation, cardiac valvular disease, polycythemia, thrombocythemia, estrogen treatment, hemodynamic factors).

Contraindications to aspirin,

Need for antiplatelet drugs.

Angiographic evidence of tight stenosis of the origin of the internal carotid artery or the vertebral artery.

Residual deficits severe enough to preclude attendance at the outpatient clinic.

Diagnosis was based on the clinical symptoms and on extensive documentation of the ischemic episode, which was classified as TIA, completed stroke or as a probable lacune. Cerebral angiography and CT scans were optional. ECG, chest x-ray, blood chemistry and hematology determinations were done in all patients to exclude comorbid conditions.

Enrollment:

Six hundred and four (604) patients were randomized in 4 centers between October 1975 and December 1, 1978 to receive double-blindly, t.i.d. capsules containing either:

330 mg of aspirin (198 patients),
330 mg of aspirin + 75 mg of dipyridamole (202 patients) or placebo (204 patients)

The patients were reevaluated at least every 4 months by means of detailed history and neurological and cardiovascular examinations. Routine laboratory examinations and ECG were

performed at least once a year. Total follow-up period was 3 years.

End Points: Fatal and nonfatal cerebral infarction. The ischemic nature of the stroke was established clinically based on the nature and duration of the clinical symptoms and ancillary investigations. After 1977 CT scans were also performed.

Baseline Characteristics: No significant differences were reported. The patients were 70% men and had a mean age of 63 years. The entry episode was stroke in 84% of the cases and TIA in 16% of them. Most patients (81-82%) had 1-3 risk factors (hypertension, diabetes, hyperlipidemia, high serum uric acid levels, Hct >50% and cigarette smoking). There were also no significant differences regarding the characteristics of ischemic effect at entry. The majority of the patients, 41-52%, had minor sequelae, 23-35% had moderate sequelae and 8-10% had no sequelae from their previous stroke.

Risk Factors: There were no significant differences regarding the risk factors (Table 2 of the publication) or their association (No. of risk factors in each group). Most patients (59-65%) suffered from hypertension. An equal percentage (62-66%) were cigarette smokers. The only significant difference which was reported involved the duration of hypertension before the entry episode: 12 years in the placebo group, 10 in the aspirin group and 9 in the aspirin-dipyridamole group ($p < 0.05$). Table 2 also shows that the placebo group had more patients with a history of MI (10) than the aspirin (7) or the combination group (4). However, these differences were not reported to be significant.

TABLE 2 *Risk Factors* and Cardiovascular Comorbidity*

	3 groups (604) %	Placebo (204) %	Aspirin (198) %	Aspirin dipyridamole (202) %
Arterial hypertension	63	63	65	59
Diabetes	22	24	22	25
Hyperlipemia	26	27	27	25
High serum uric acid	20	17	23	20
Hematocrit >46%	28	34	24	26
>50%	6	4	6	7
Cigarette smoking	64	65	62	66
None of the above	10	10	10	11
Angina pectoris	8	7	8	8
Myocardial infarction	7	10	7	4
Cardiac failure	2	2	2	1
Peripheral arterial disease	7	8	5	9

*For all risk factors, percentages indicated in the table include previous positive history for these factors and factors discovered at entry according to the following definitions: arterial hypertension: blood pressure ≥160–100 mm Hg at least twice; diabetes: FBG >7 mmol/l; hyperlipemia: CT >7.74 mmol/l and/or TG >2.05 mmol/l; high serum uric acid: men: >476 mmol/l; women: >387 mmol/l; cigarette smoking: >1 cig/day for more than one year.

Compliance was evaluated from information supplied by the patients and from urine salicylate determinations during the last 18 months (the salicylate results were unavailable to the responsible neurologist). It was reported that 82% of the placebo patients, 83% of the aspirin patients and 70% of the aspirin-dipyridamole patients were compliant.

RESULTS

Sixty-six patients (11%) were discontinued (moved away, lost to follow-up, uncooperative). There were no significant differences between the groups regarding the numbers of these patients (21:25:20).

The endpoint events which occurred in these patients during the 3 year period of the study were as follows:

Ischemic Strokes:	Placebo	Aspirin	Aspirin-Dipyrid.	
Non-fatal	14.2%	8.6%	7.4%	
Fatal	1%	0	1.5%	
Total	15.2%	8.6% (<0.05)	8.9%	(p<0.06)
Deaths from other causes	3.4%	5%	4%	
Vascular diseases Other than ischemic stroke*	7.8%	4%	2.5%	(p<0.04)
G.I. Effects (Total)	3%	9%	9%	(p<0.03)
Minor side effects (other)	14%	20%	16%	(NS)

*cerebral hemorrhage, MI, peripheral arterial disease, pulmonary embolism, atrial fibrillation.

The difference in strokes between aspirin and placebo was significant ($p<0.05$). The difference between placebo and the combination group was not quite significant ($p<0.06$). There was no significant difference between aspirin and the combination. Comparison of the placebo to the two treatment groups combined was significant to the 0.02 level. Five of the 66 patients who suffered a stroke (8%) died, 77% had major sequelae and 10% had a complete recovery. There was no significant difference in deaths between the groups. The incidence of GI side effects (ulcer, hemorrhages and upper abdominal pain), however, was 3 X higher in the aspirin groups ($p < 0.05$). The greatest differences were observed in the incidence of ulcer and hemorrhage (1:7:9, respectively, $p < 0.01$).

A significant difference between the groups was also found regarding the incidence of myocardial infarction. There were 11 cases of MI in the placebo group, 4 in the aspirin group and 3 in

the combination group ($p<0.05$). However, as mentioned earlier, the placebo group had more patients with a history of MI at baseline than the other groups (10:7:4 respectively; Table 2). I wonder whether these differences were taken into consideration when the results for myocardial infarction were analyzed.

There were no significant differences in intracranial bleeding (2:2:1 for placebo, ASA, ASA+ dipyridamole). Subgroup analysis by sex indicated that aspirin reduced the incidence of stroke in women by 57% (from 14% to 6%) and in men by 32% (from 19% to 13%) but there were also fewer strokes in women in the placebo group than they were among the placebo men (14% vs 19%). The difference for women was not statistically significant. It was only a trend.

Evaluation: We have no details (copies of case reports) from this study and we do not know how accurate the data are. At its face value this old (1975-8), relatively small, French study showed that aspirin at 1 g/day can reduce the incidence of stroke (the results for MI are debatable) significantly in patients who had experienced a previous stroke (84% of them) or TIAs (16%). Subgroup analysis by sex showed a trend for women for the prevention of stroke. The number of women in the entire study was small (184) i.e. the study had not enough power to detect a significant effect for women.

AICLA is the only study that showed that aspirin can significantly reduce the incidence of stroke. All other studies (UK-TIA, DUTCH-TIA, SALT) have shown significant differences for composite endpoints (stroke TIAs; non-fatal stroke or death; non-fatal stroke, non-fatal MI or death vascular or total) not for stroke alone. Considering the size of AICLA (the aspirin and the placebo group had 198 and 204 patients respectively) its results are unexpected.

2. **Antiplatelet Trialists' Collaboration** (Brit Med J 48:320, 1988).

In this Publication the Trialists evaluated 25 randomized clinical trials of antiplatelet treatment for patients with a history of transient ischemic attacks (TIAs), occlusive stroke, unstable angina, or MI. These trials included 29,000 patients with 3000 deaths.

Thirteen of the trials were concerned with patients who had a history of cerebrovascular disease, TIAS, stroke, or amaurosis fugax. Twelve other studies were concerned with patients who had a history of myocardial infarction (10) or unstable angina (2). In 6 of the cerebrovascular trials and in 5 of the coronary trials antiplatelet agents other than aspirin or combinations of

aspirin with other antiplatelet agents were used.

I have summarized below the results regarding the occurrence of non-fatal stroke in the studies where aspirin was used alone. (I have excluded the results of AICLA from these tabulations because I discussed this study previously). I have also excluded the results of the Cardiff and the GAMIS studies because the number of strokes which occurred in these studies is not stated in the trialist paper. On the other hand, I have added the results of ISIS-2 among the coronary trials.

a). Cerebrovascular Trials

			Non-Fatal Strokes		
	Dosage mg/day	Duration years	Aspirin	Placebo	Difference
UK-TIA	1200, 300	4	139/1621	92/0814	-2.7%
Canadian Cooper.	1300	2	17/0144	17/0139	0.4%*
Swedish Stroke	1500	2	23/0253	18/0252	+2.0%
AITIA (Med)	1300	1	10/0088	12/0090	-1.9%*
(Surg)	1300	1	2/0065	7/0060	-8.6*
DCS (Danish Study)	1000	2	14/0101	12/0102	+2.1%
German TIA	1500	2	2/0030	3/0030	-3.3%
TOTAL/MEAN		2	**207/2272**	**161/1487**	**-1.7%**
			9.1%	**10.8%**	

$X^2 = 2.998$; $p<0.1$

Odds ratio = 0.8256 95% CI (0.6644, 1.0259); 2p=0.0833

b). Coronary Trials (I have included also the results of ISIS-2):

AMIS	1000	3	27/2267	46/2257	-0.85%
CDP-A	972	2	9/0758	8/0771	+0.15%
GDR	1500	2	6/0672	14/0668	-1.21%
VA	324	0.25	3/0687	2/0701	+0.15%
ISIS-2	162	35 ds	27/3492	51/3489	-0.69%
TOTAL			**72/7876**	**121/7886**	**-0.62%**
			0.9%	**1.5%**	

$X^2 = 12.53$; $p= <0.001$

Odds ratio = 0.5921, 95% CI (0.4415, 0.7940), 2p=0.0007

* These data were extracted from the individual published reports.

Conclusions: These results suggest that aspirin reduced the incidence of non-fatal stroke by 1.7%, from 10.8% to 9.1% in the patients, who had previous cerebrovascular events. My calculations show that this reduction is not statistically

significant (probably, this is because the number of patients involved is small and there is not enough power to detect the significance of the small aspirin effect). Determination of the odds ratio by Dr. Sankoh, FDA statistician, confirmed my statistics (odds ratio 0.8256; 2p=0.0833).

If we add the results of the SALT study to the sum of the cerebrovascular studies listed in the Trialist publication, the statistical power is increased and the difference between aspirin and placebo becomes significant:

Non-Fatal Stroke

	Dosage mg/kg	Aspirin	Placebo	Difference
Sum of 7 studies		207/2272	161/1487	-1.7%
SALT	75	77/0676	102/0684	-3.5%
NEW TOTAL		**284/2948**	**263/2171**	**-2.5**
		9.6%	**12.1%**	

$X^2 = 8.06$ $2p<0.01$

Odds Ratio: 0.7734, CI (0.6474 0.9239), 2p=0.0051

The incidence of stroke in the patients who had a history of **coronary events** was much lower, 1.5%. Aspirin reduced this incidence to 0.9%. This reduction seems to be highly significant because the number of patients involved in this comparison was very large, > 15,000.

The dosage of aspirin in all the cerebrovascular studies except in SALT was high. It varied from 1000 to 1500 mg/day. In the UK-TIA study aspirin was used at a low dosage (300 mg/day) in parallel with the higher 1200 mg dose. No significant differences between the two dosages were found regarding effectiveness but the incidence of side effects, especially G.I. effects, was higher with the larger dose. The aspirin dosage in SALT was 75 mg/day.

In 3 of the coronary trials the dosage was also high. Only in the VA and ISIS-2 studies aspirin was used at relatively low dosages, 324 and 162 mg/day respectively.

Results from Fatal Stroke alone have not been summarized in the Trialist paper. Fatal stroke was reported as a composite endpoint, combined with other vascular events (MI or death) and it is not possible to separate its value from the total result.

I have summarized below data from the published reports of some of the individual studies:

a) Cerebrovascular Trials:

		Dosage mg/day	Fatal Stroke Aspirin	Placebo	Difference %
UK-TIA		1200, 300	37/1621	15/0814	+0.5
Canadian		1300	5/0144	3/0139	+1.31
SALT		75	16/0676	10/0684	+0.9
AITIA	(Med)	1300	1/0088	2/0090	-1.08
	(surg)	1300	0/0065	1/0060	-1.67
Total			**59/2594**	**31/1787**	**+0.54**
			2.27%	**1.73%**	

X^2 = 1.53 (N.S.) p<0.25
Odds Ratio = 1.318, 95% CI (0.8498, 2.0452), 2p=0.2195

b) Cardiovascular

ISIS-2	162	**20/8492**	**30/8489**	**-0.11%**
		0.24%	**0.35%**	

X^2 = 2.01; p>0.1
Odds Ratio = 0.6656, 95% CI 0.3777, 1.1732), 2p= 0.1592

If ISIS-2 is combined with the preceding studies, the totals will be as follows:

Total	**79/11086**	**61/10276**	**+0.12**
	0.71%	**0.59%**	

X^2 = 1.16; p>0.25
Odds Ratio = 1.202, 95% CI (0.8596, 1.6806), 2p=0.2826

The means show that the incidence of fatal stroke in the cerebrovascular trials was somewhat higher in the aspirin group. The difference does not appear to be significant but it shows that aspirin may be harmful if we consider millions of people using it for a long time. It is possible that while aspirin can prevent some occlusive strokes it may increase the incidence of brain hemorrhage.

B. Prevention of Primary Stroke.

Two clinical trials have been published so far regarding the use of aspirin for the prevention of primary cardiovascular events, the British and the U.S. Physicians' trials. I have summarized below the results of these studies regarding stroke.

The British Male Doctors Study (Brit. Med. J.296;313, 1988) included 5139 apparently healthy male physicians and lasted for 6 years. Aspirin was used at 500 mg/day.

First Event/10,000 man years

	Aspirin	**Placebo**
Number of Patients	3429	1710
Non-fatal Stroke:	32.4	28.5
Fatal Stroke (Hemorr.)	5.3	4.2
(Occlusive)	4.3	3.2
Unknown etiology	6.4	5.3

According to the published report the differences were not significant.

The aspirin arm of the U.S. Physicians' Health Study (N Engl J Med 318:262, 1988) included 22071 apparently healthy male physicians and lasted for 5 years. The dosage of aspirin was 325 mg/every other day. The results on stroke were as follows:

	Aspirin	**Placebo**	P-Value
No of Subjects	11037	11034	
Non-Fatal Stroke	110	92	0.20
Fatal Stroke	9	6	0.43
Total	119	98	0.15
(Person-years)	(54650.3)	(54635.8)	

Conclusions: Both studies show that aspirin increases somewhat the incidence of primary stroke both fatal and non-fatal. The differences, however, are not significant. We should ask our statisticians to do a metaanalysis combining the results of both studies, if it can be done with the data we have.

GENERAL CONCLUSIONS:

Effect of Aspirin on the Prevention of Secondary Stroke:

a) Non-Fatal Stroke:

Patients with a History of Cerebrovascular Events: The metaanalysis of 6 aspirin studies included in the Antiplatelet Trialists' report indicated that aspirin can reduce the incidence of stroke by 1.7% (from 10.8% to 9.1%) **in patients who have a history of cerebrovascular events** (stroke, TIAs, amaurosis fugax). However, for the effect to become significant it was necessary to add the results of the SALT study as well in order

to increase the total number of patients to be included in the comparison (to 5,000) and thus increase the difference between the groups to 2.5% and also the statistical power. It appears that a little over 3,500 patients were not sufficient to show whether the aspirin effect is significant.

The need for a large number of patients can explain the fact that none of the individual studies by itself was able to show a significant aspirin effect on stroke considered alone as an end-point, with the exception of AICLA. AICLA was a small study with approximately 200 patients in each group but it showed that aspirin can **significantly** reduce the incidence of stroke in patients with a history of cerebrovascular events. The aspirin effect was about 2-3x greater in AICLA than it was in the other studies combined (it decreased the incidence of stroke by 5.6% vs 1.7% and 2.5% of the sum of the other studies). We do not know why the 400 patients in AICLA were sufficient to show a significant effect, while 3,500 patients in 7 other studies combined were not enough. Was the AICLA population different? Was the fact that AICLA had lasted for 3 years while the other studies had lasted on the average for 2 years? The UK-TIA study had lasted for 4 years and had 2435 patients, 6 times more than the aspirin part of AICLA, and yet it could not show a significant effect on stroke alone. Non-fatal stroke was combined with non-fatal MI, vascular death, and non-vascular death to obtain a significant difference in the UK-TIA study. Even a combination of stroke with vascular death was not sufficient to show a significant difference. Similarly, SALT had more than 3 times the number of patients/group than AICLA had. Yet the difference in the occurrence of strokes (fatal and non-fatal combined) between aspirin and placebo was not significant.

b) <u>Patients with a History of Cardiovascular Events:</u> The incidence of non-fatal stroke in these patients was much lower (1.5% only) than it was in the patients with a history of cerebrovascular disease (10.8%). Aspirin reduced this incidence to 0.9%. This 0.6% reduction was statistically significant (>15,000 patients were included in these studies). Very small effect but statistically highly significant. How good is it clinically? Aspirin will probably prevent 6 non-fatal strokes in a population of 1000 patients.

Fatal Stroke:

Aspirin does not seem to affect the incidence of fatal stroke significantly. If anything, it appears to increase a little (0.54%) its incidence in patients with a history of cerebrovascular events. The incidence of fatal stroke was very small in both types of patients especially in those suffering from cardiovascular events.

Prevention of Primary Stroke:

Aspirin appears to be **rather harmful** regarding the prevention of both fatal and non-fatal primary strokes. The differences from placebo were not significant because strokes are very rare among healthy individuals. If we want to get significant differences one way or the other, it would probably be necessary to use hundreds of thousands or a million of subjects. Impractical and probably counterproductive.

Labeling

Indications:

Considering the evidence that we have now, aspirin can be approved for the prevention of stroke in patients who have a history of cerebrovascular events or coronary heart disease. The effect is statistically highly significant but clinically rather negligible or controversial.

In patients with a history of cerebrovascular disease, aspirin might be able to prevent 25 non-fatal strokes among 1000 patients but it will cause un excess of 5 fatal strokes among them i.e. it might kill 5 of these patients in order to prevent the occurrence of 25 non-fatal strokes among the 1000 patients. Regarding patients with a history of coronary heart disease aspirin may be able to prevent 6 non-fatal and one fatal stroke among 1000 patients.

For the prevention of primary strokes i.e. prevention of strokes in apparently healthy individuals, aspirin cannot be indicated because it appears to be rather harmful. It may cause 3 fatal and up to 18 nonfatal strokes in 55,000 person-years.

Dosage: Currently aspirin is approved for the reduction of risk of recurrent TIAs or stroke in patients with a history of these events at a dosage of 650 mg bid.[2/d] This dosage was used in most of the studies discussed in this review.

However, the UK-TIA study provided evidence that aspirin at 300 mg/day can be as effective as at 1200 mg/day in reducing the combined incidence of non-fatal stroke, non-fatal MI, vascular death or non-vascular death. In SALT aspirin was used at 75 mg/day and this dosage was sufficient to reduce the incidence of stroke and total death significantly compared to placebo. [In the DUTCH-TIA study the aspirin was used in dosages of 30 and 283 mg/day but there was no placebo and reliable conclusions regarding the effectiveness of aspirin cannot be drawn from this study].

If we accept the results of these studies at their face value, we should recommend that for the prevention of stroke and the other events in patients with either a history of cerebrovascular or cardiovascular disease the dosage of aspirin can vary from 75-325 mg/day. All patients do not have the same needs. Some may require more aspirin, while others can be protected with less. The incidence of side effects (calculated per year) increases little within this range (see MOR of Jan. 22, 1992). The incidence of intracranial hemorrhage increases even with the smallest aspirin dosage but it does not increase much further when the dosage is increased to 300 mg/day.

Women: None of the studies or the metaanalysis showed that aspirin can significantly reduce the risk of having a stroke among women. In the UK-TIA study women who received aspirin had fewer major strokes than women who received placebo but they also had more disabling strokes than the latter. Only AICLA showed a trend in favor of aspirin for women but the results of this study seem to me unreliable as I explained before.

It seems to me that the lack of evidence that aspirin can have the same effect on women that it has been shown to have on men, is due to the fact that considerably fewer women than men (1:3 or none) have participated in the aspirin studies. The effect of aspirin on stroke is so small that at least 4,000 patients must be included in a study or in a metaanalysis in order to demonstrate it. None of the studies had that many women.

E. Triantas, MD

Eugenie Triantas, M.D.

cc:
HFD-180/Consult File
HFD-180/SFredd
HFD-180/ETriantas
f/t deg: 7/15/92/7/23/92
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SEP 27 1993

Note to:

Dr. Weintraub
Dr. Bowen

Subject: ASA 1° Prevention

We did not recalculate results omitting all prior MI's because those patients were not all identified. Some estimated corrections were made, however, assuming 8% of the population had a prior MI. As I understand Dr. Fredd's note, depending on assumptions, the p-value may fall below (above) p=0.0027, the "stopping rule" p-value. But it isn't much worse at 0.0036. Moreover, the overall reduction in this study of about 44% in fatal and non-fatal MI, is larger than most of the studies of 2° prevention show, so that this subgroup is not likely to be pulling the result along.

Robert Temple, M.D.

M E M O R A N D U M

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

DATE: SEP 13 1993

FROM: Director
Office of OTC Drug Evaluation (HFD-800)

TO: Director
Office of Drug Evaluation I (HFD-100)

SUBJECT: Aspirin for Primary Prevention of Acute Myocardial-Infarction

Thanks for your thoughtful, helpful comments. Your reasoning supports what many of us think, although we do wish that a simple primary preventative treatment had been shown safe and effective.

There remains one point that the ~~Physicians Health Studies people~~ have not clarified. By error, a number of physicians who had had an acute myocardial infarction were included. I have seen a draft paper concerning this group. As expected, the aspirin treated physicians had statistically significant favor repeat myocardial infarctions (see Stats review page 6). about 15%

What I do not know was whether or not that secondary prevention group is also included in the overall results. Of course, if they are, the data on infarctions would have to be recalculated. Because aspirin was effective as secondary prevention and the total differences in myocardial infarction is, at best, 100 (139 vs 239 in table 1 of the New England Journal of Medicine report) removing the highly effective group's data from the numerator may importantly narrow the difference with little effect on the denominator. In other words a large part of the "action" might have been in the secondary prevention, not the primary prevention group.

Until that point is settled, I can't accept the primary prevention claim even if the NHS is positive in favor of aspirin.

Thanks again.

Linda O Arntzenius
for
Michael Weintraub, M.D.

Note, also, that the MI effect in this study is bigger than in the 2° prevention studies

Mike: They are included. This is referred to in Dr Temple's review. I do not believe it alters the major finding (reduction in MI) but it does (if you leave them out) make the overall result less impressive. I think if NHS is yes we're OK on the finding (but maybe still no survival effect). RT

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	Coordination		Justify		

9/15/93 Bob – I attach copies of the package and our reviews. We made certain assumptions, and thought M.I.'s to be appropriate endpoints in M.I. pts but we [illegible] not sure (for the [illegible]) [illegible] [illegible] of the [illegible] replication! Steve

REMARKS

I was about to send this to Mike, but didn't have the review pkge (we have [illegible] does). Didn't we recalculate the AMI data leaving out the 15% (I recall) who had a prior MI by ECG and finding the outcome unchanged.

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M E M O R A N D U M

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

DATE: SEP 13 1993

FROM: Director
Office of OTC Drug Evaluation (HFD-800)

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Thanks again.

Linda B Weintraub
for
Michael Weintraub, M.D.

M E M O R A N D U M

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

DATE: SEP -2 1993

FROM: Director, Office of Drug Evaluation I, HFD-100

SUBJECT: Aspirin for Primary Prevention of Acute Myocardial-Infarction

TO: Dr. Michael Weintraub, HFD-800
Director, Office of Over-the-Counter Drug Evaluation

I. Introduction

Aspirin at about 300 mg/day, perhaps less, clearly prevents recurrent myocardial infarction, and prevents first infarction and death in patients with unstable angina. These claims have been accepted by FDA, as has prevention of stroke in patients with documented TIA's. Overviews (metaanalyses of clinical trials) suggest that first AMI and stroke are also prevented in patients with prior claudication, AMI, or stroke, i.e., patients with clinically significant arterial occlusive disease of some vascular bed. No claim for this use has been accepted by FDA nor sought by a sponsor, perhaps because it has little treatment implication. (If patients are already treated as secondary prevention for MI or stroke, it doesn't add much to say it also prevents the other event. Perhaps use in claudicants could be appealing, but no one has asked.) So far as I am aware, no study has shown a reduction by aspirin in thrombotic events in patients with ordinary angina of effort, a group with clear CAD, but not with a recognized infarction. I don't believe this group has been well-studied, which is somewhat surprising.

The Physicians Health Studies (U.S., Great Britain) are in a population that is even healthier (vascularly) than an angina population; they have no evidence of CAD at all, nor evidence of occlusive disease of any other vascular bed. Aspirin has at least one recognized "downside", it can cause serious bleeding in the GI tract and intracerebrally. It is thus not obvious a priori whether it will provide a net benefit in a cardiovascular low-risk population. The two Physicians Health Studies (PHS) were designed to examine that question. These studies are considered in Dr. Fredd's review of November 16, 1989 and in attached MOR's and a statistical review. The Division recommends non-approval of the primary prevention claim.

II. Inconsistency Between U.S. and U.K. Studies

It is often stated in reviews that the British Physicians Study was poorly done (because of crossovers: by the halfway point of the study 30% of patients randomized to ASA were no longer taking it and about 2% of patients each year who were randomized to placebo began to take ASA) and was too small (about 5000 patients vs 22,000 in the U.S. study) to matter, but I do not agree with either contention. Considering endpoints, the study was not small and a considerable fraction of patients remained on assigned treatments. Its failure to replicate the U.S. findings is therefore a serious problem. I realize some analyses indicate that the confidence intervals of the two studies overlap so that they are not "statistically inconsistent". This is apparently the case for the non-fatal MI endpoint, but non-fatal MI is not the right endpoint to consider. There is no particular reason to believe aspirin prevents non-fatal infarction, but has no effect on fatal ones. In fact, in both studies, the effects of aspirin are the same (large effect in U.S.; no effect in U.K.) on fatal and non-fatal AMI's. The U.K. paper describes the CI for the effect of ASA on total MI as -27% to +24%. For the U.S. study, the CI for total MI was 0.45 to 0.70 (a lower bound of about a 30% reduction). The CI's thus <u>do not</u> overlap; there is a true failure to replicate.

The U.K. study was not really small when one counts total infarction (fatal and non-fatal); for some reason, MI's were far more fatal in the U.K. than in the U.S. The U.S. study had a total of 378 MI endpoints. The U.K. study had 257 definite fatal and non-fatal infarctions (283 if you count possible non-fatal infarction). The U.K. study there had about 3/4 of the number of U.S. endpoints, hardly small, and, as noted the CI's do not appear to overlap. My principal reason for concluding that we should not accept the primary prevention claim is the failure of what seems to be a second well-controlled study to replicate the finding of the U.S. Physician's Health Study.

III. The Findings of the U.S. Study

Interpretation of the U.S. Study is complex and will never be wholly satisfactory. A few things are very clear. It was intended to be a mortality study but the dogged healthiness of U.S. Physicians reduced the rate of mortal endpoints to the point where the study had little or no chance of showing a survival effect. [This is not absolutely certain, of course; the population was aging and it would seem that having 44% fewer MI's could lead to some long-term benefit, such as less CHF or fewer arrhythmias. On the other hand,

almost everyone who had a first MI went on aspirin, so that any late impact would have to arise entirely from the difference in first infarctions, probably a long shot. In any event, the independent, very highly-qualified DSMB of the PHS concluded success was unlikely.] In addition, the study showed a dramatic effect on heart attacks, fatal or non-fatal, an effect that certainly could withstand corrections for early looks or multiple endpoints.

Once one leaves the primary endpoint of cardiovascular mortality (and on this there is not even a strong trend, 81 aspirin vs 83 placebo), it becomes difficult to say just what the best endpoint is. Given the initial intent to include both cardiac and cerebrovascular deaths one could argue that the most correct new endpoint should be all fatal and non-fatal cardiovascular events, i.e., non-fatal MI and stroke plus total cardiovascular mortality. The trialists do not present an analysis of this end point, and it is not possible to use their published data to calculate this endpoint in the usual way, i.e., with the first endpoint only as the one counted. It is clear that the stroke end point was heading the wrong way, with total 119 ASA vs 98 placebo.

It is not clear what the result of this endpoint was. (I am forwarding this memo without resolving this question because it is not critical to my conclusion but will send this memo to Stats and HFD-180 for further discussion, if needed.) In the Stat review (p. 4) the relative risk is given as 0.82 (307 ASA vs 370 placebo, p=0.01). This is considered <u>not</u> to meet the stopping rule p-value of 0.0027 and is not yet adjusted for multiple endpoints. The published study report shows:

	ASA	Placebo
Total CV Deaths	81	83
NF Stroke	110	92
NF MI	129	213
	320	388

This value is not reduced by subtracting second events and is, therefore, compatible with the 307 vs 370 value on p. 4 of the Stats review. The difference between treatments is almost the same.

Table 4 of the Stat review seems to show a different result for the combined endpoint, with RR of 0.7454 and a p-value of 0.0009, certainly impressive. This appears to be an analysis using a logistic regression analysis. It is not clear which analysis is considered correct by Biostats.

It is not clear what the right multiplicity correction is (how many endpoints really would be plausible and how independent are they?), and it is not at all clear that the p=0.0027 stopping rule value is the p-value of interest for endpoints other than the one causing stopping (which was total AMI, in this case). What <u>is</u> clear, however, is that the only endpoint favorably affected is MI (fatal or non-fatal), that the British Study does not replicate it, and that CV mortality is not favorably affected at all. Should the Nurse's study replicate the MI finding, I would find the evidence for reduction of MI persuasive. We would then need to consider the evidence of <u>net</u> benefit.

IV. Conclusion

We cannot now endorse a claim for primary prevention of AMI in any population.

Robert Temple

Robert Temple, M.D.

HARVARD MEDICAL SCHOOL
Department of Medicine

IND AMENDMENT SA

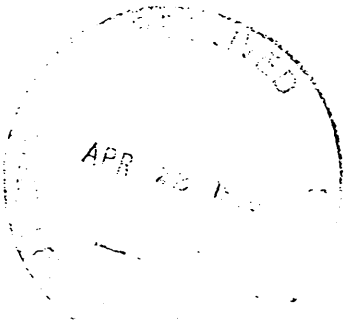
BRIGHAM AND WOMEN'S HOSPITAL
A Teaching Affiliate of Harvard Medical School

ORIGINAL

Watch Schwartz 5/15/86

Please Reply to:
Physicians' Health Study
55 Pond Avenue
Brookline, Massachusetts 02146
(617) 732-4969

April 9, 1986



Natalia A. Morgenstern
Supervisory Consumer Safety Officer
Division of Cardio-Renal Drug Products
Office of Drug Research and Review
Center for Drugs and Biologics
Food and Drug Administration
Rockville, MD 20857

Dear Dr. Morgenstern,

Pursuant to our telephone conversation of several weeks ago, I am writing to inform you of two changes in our use of aspirin as part of the Physicians' Health Study, under IND No. 17275 held by Dr. Hennekens. One change is that when physicians participating as subjects in the trial complain of gastro-intestinal symptoms attributable to the aspirin (or aspirin placebo), we send them enteric coated aspirin or placebo for the remainder of the trial (which is ongoing). We employ this policy to maximize compliance to the treatment regimen.

The second change relates to a substudy of the main trial in which, in a group of volunteers not participating in the Physicians' Health Study, we are seeking to determine the lowest effective dosage of regular and enteric coated aspirin to inhibit platelet aggregation. As part of this study, subjects will take various doses of regular or enteric coated aspirin up to a maximum of 325 mg per day. This substudy will last a maximum of three months.

Yours sincerely,

Meir Stampfer

Meir Stampfer, M.D.
Assistant Professor of Medicine
Harvard Medical School
Project Director, Physicians' Health Study

/srs

cc: C. Hennekens

JUL 5 1988

Charles H. Hennekens, M.D.
Physician's Health Study
55 Pond Avenue
Brookline, Massachusetts 02146

Dear Dr. Hennekens:

We have had internal discussions of the data we will need to review the U.S. Physicians Health Study. You can, from your knowledge of the study, probably expand on this list, but at this time we would expect to want access to:

1. The baseline (entrance) characteristics of the subjects to the extent available:

   a. personal medical history
   b. family history
   c. cholesterol levels
   d. triglyceride levels
   e. fasting glucose levels
   f. blood pressure
   g. smoking habits
   h. exercise habits
   i. other medication (such as beta blockers, calcium channel blockers, nitrates)
   j. caffeine consumption
   k. weight, expressed as % of recommended body weight for age and sex

2. Definition of the criteria of the end points, including criteria for the diagnosis of fatal and non fatal myocardial infarction, sudden death, and other categories of cardiovasacular death or non-fatal outcomes, as well as criteria for diagnosing and distinguishing between thrombotic stroke and hemorrhagic stroke.

3. Compliance information, including serum thromboxane levels, if available.

4. Results (outcomes) initially reported, criteria for committee reclassification and results as reclassified.

5. Case reports of all patients with evaluable end points.

6. Case reports of all patients with serious adverse reactions.

7. Study protocol.

8. Specification of statistical method used for each analysis.

9. Specification of statistical software used (e.g. SAS, BMDP)

10. If data analysis were done in SAS, appropriate SAS codes for each analysis should be provided. For example, SAS codes used to create data sets or to analyze data sets should be provided.

11. Listing of variables in data sets, definitition of variables, and hard copy of the first 100 records for each data set for the purpose of validation.

12. Magnetic tape specification for submitting data:
    a) in SAS data format,
    b) IBM tape (standard label or non-label),
    c) 6250 BPI
    d) include SAS library name,
    e) include SAS data set names in SAS library,
    f) procedures used to create tape.

We would also appreciate knowing the software needed to analyze the data tapes.

Let me know if any of this presents a problem.

Sincerely yours

Robert Temple, M.D..
Director
Office of Drug Evaluation I
Center for Drug Evaluation and Research

cc:
IND 17,275
HFD-180/GEN. COR. File
HFD-180/Reviewers
HFD-180/MPetersen/5/13/88
agb/5/13/88/1143d
RDinit:SFredd/5/13/88
ETriantas/5/13/88
GChi/5/27/88
RTemple/6/22/88
General Correspondence

BRIGHAM AND WOMEN'S HOSPITAL
Harvard Medical School
Department of Medicine
Channing Laboratory

Please reply to:
Physician's Health Study
55 Pond Avenue
Brookline, Massachusetts 02146
(617)732-4969

Robert Temple, M.D.
USFDA
Parklawn Building, 14B45
5600 Fishers Lane
Rockville, MD 20857

August 4, 1988

Dear Bob:

Thank you for your letter of July 5, 1988. As you know, we are currently working on the preparation of the final report for the aspirin component of the Physicians' Health Study. Our efforts are focused in two areas: (1) confirmation of all major cardiovascular events reported as occurring on or before January 25, 1988, the date the physicians were unblinded as to their treatment assignment in the aspirin component and (2) working out the specific analyses needed for the final report. Currently, we are negotiating with Bristol Myers for the additional financial support needed to do the extra work required by your request. As soon as the funds are available, we can begin preparation for this submission to the FDA.

Of the baseline variables which you mentioned, triglyceride, fasting glucose and caffeine consumption are not available. We did collect self reported blood pressure, available on 88% of the sample, and cholesterol level, available on 36% of randomized subjects. In addition, we have data on alcohol use, some dietary information, and family history of MI. The compliance data are primarily self report, with small subsamples of serum thromboxane levels collected in two geographic areas at two different points in time to validate the self reports.

From our recent conversations, I understand that you are also interested in analyses that combine the data of the US Physicians' Health Study with the British Doctors' data. We would certainly be willing to include such analyses in our submission, but would, of course, need the collaboration of Richard Peto, which would include a computer tape of the British data.

As soon as the resources become available, I will be in touch to finalize the specifics of your request and an appropriate timetable for the work.

Kindest personal regards.

Yours sincerely,

Charles H. Hennekens

cc: J. Migliardi
R. Peto

ORIG N(RD)
732-4975

BRIGHAM AND WOMEN'S HOSPITAL
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Department of Medicine
Channing Laboratory

I17;275

June 9, 1989

STRICTLY CONFIDENTIAL

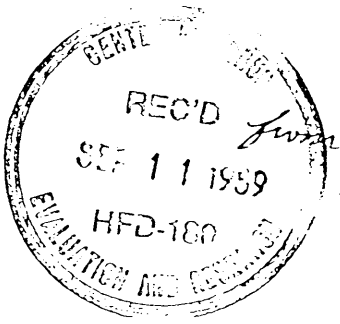
Steven Fredd, MD
Director
Division of Gastrointestinal and
Coagulative Drug Products
Food and Drug Administration
5600 Fishers Lane
HSD 180, Room 1092
Rockville, MD 20857

Dear Dr. Fredd:

I am writing in response to your and Bob Temple's request for more detailed information on the data analyses of aspirin and risks of cardiovascular disease in the Physicians' Health Study database. The analyses that went into our final report were supervised by Fran Stubblefield, systems/analyst and Director of our research data processing group. Before releasing this detailed information and the final report, we had the entire set of analyses independently repeated by Martin VanDenburgh, a senior systems/analyst with over 15 years of research programming experience. Mr. VanDenburgh was given the raw data and the set of processing rules and definitions. He then reprogrammed the entire analysis. His results matched the original analyses exactly. Thus, I am now pleased to forward you the information you requested.

Attached is a loose-leaf binder which contains the following:

Attachment I	Copy of the recent Report of the U.S. Preventive Services Task Force concerning low-dose aspirin in the primary prevention of myocardial infarction
Attachment II	Strictly confidential copy of the Physicians' Health Study Final Report which is currently in press in NEJM and scheduled for publication on July 20, 1989
Attachment III	Strictly confidential copy of the review paper on aspirin in secondary and primary prevention of CVD which is in press in Circulation



From Dr Fredd this date

Attachment IV	Copies of the PHS Questionnaires
Attachment V	Description of the PHS procedures for following, verifying, recording and selecting for analyses endpoint information
Attachment VI	Description of the PHS procedures for processing side effects and following reported bleeding events, liver disease and ulcer
Attachment VII	A complete list and definitions of variables used in the PHS Final Report
Attachment VIII	Copy of the SAS routine used to compute person years of exposure
Attachment IX	Description of PHS data analysis procedures and statistical formulas
Attachment X	Physicians' Health Study Protocol

I would certainly be willing to have you or one of your staff visit our research group and examine the endpoint files, if you feel that would facilitate your review of our results. Please let me know if you have any additional questions or requests.

Kindest personal regards.

Yours sincerely,

Charles H. Hennekens

cc: R. Temple, MD (no attachments)

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MEMORANDUM OF TELECON

DATE: June 23, 1989

APPLICATION NUMBER: IND 17,275

BETWEEN:
Name: Frances Stubblefield
Phone: (617) 732-4973 (or 732-4985)
Representing: Dr. Charles Hennekens

AND
Name: Thomas H. Hassall, Supervisory CSO
Div. Gastrointestinal and Coagulation Drug Products, HFD-180

SUBJECT: U.S. Physician's Health Study

Dr. Hennekens responded on June 9, 1989 to a July 5, 1988 request from information on the U.S. Physician's Health Study. Dr. Fredd asked me to contact Dr. Hennekens to determine whether the remainder of the information requested in the July 5, 1988 letter would be possible to submit since the June 9 submission did not contain responses to each item. Dr. Hennekens was out of the country; my call was returned by his assistant, Frances Stubblefield.

Ms. Stubblefield gave me the following clarifications:

1. Most of the baseline variables requested in item 1 of the July 5 letter are covered in the final report found in Section II of the material submitted June 9. She referred specifically to page 26.

2. Some information such as thromboxane levels to confirm compliance is not available. She said this was explained in an earlier letter to Dr. Temple. What had been done were samples of about 50 of the participants in the local area (including Rhode Island) as a way to check on the validity of the self reporting. Actual compliance information was not obtained in each participant.

3. The information requested in item #2 of the July 5, 1988 letter (Definition criteria of end points) is in section V of the June 9 submission.

4. Case reports, as requested in items 5 and 6 (July 5, 1988) would be very burdensome to copy and submit. This material will be willingly made available if someone wishes to inspect the study to verify patients, as stated in the June 9, 1989 letter.

5. The study protocol, statistical method and statistical software and codes (items 7,8,9, and 10 in July 5, 1988 letter) are in the June 9 response.

6. With regard to computer tapes (item 12), Dr. Hennekens

Division Director does not want to send these. Alternatively, Dr. Hennekens would be willing to have FDA personnel visit the facility and review the information there and would provide technical support for processing specific analysis requests.

Ms. Stubblefield indicated they would provide further information if, after review of the reports and information submitted June 9, we identified the additional material necessary to satisfy our review. She indicated that, with the exception of the magnetic tapes and the case report forms, she believed the June 9 submission addressed most of the informational needs expressed in our July 5, 1988 letter.

Ms. Stubblefield was very cooperative. I agreed to convey her comments to Dr. Fredd and get back to her at a later date.

Thomas H. Hassall
6-23-89

cc:
orig (I17,275)
HFD-180 Div File

SEP 12 1989

IND 17,275

Charles H. Hennekens, M.D.
Harvard Medical School
Brigham and Women's Hospital
55 Pond Avenue
Brookline, Massachusetts 02146

Dear Charlie:

With this letter I am transmitting to you our medical and statistical review of the Physicians Health Study of aspirin to prevent first heart attack. These reports will be provided to the Cardiorenal Advisory Committee for their consideration. I believe some new issues are raised, i.e. preexisting M.I.'s in the test population, and silent infarcts, perhaps unevenly distributed between the treatment arms because of the analgesic effect of aspirin.

To address these issues you might review the database to identify all patients with non-fatal M.I.s who had evidence of previous M.I.s, remove them, and present the results of the study without them, including baseline characteristics and subgroup analyses. Since the relative risk comparisons utilize person years determination from the total cohort, for the denominator, some estimate of those with preexisting MIs in the total cohort and adjustment of person years will need to be considered.

The silent M.I. question is more difficult to assess, unless you have or could obtain previous EKGs from the participants, or obtain current EKGs from a sample of the cohort to get some estimate of the extent of silent M.I.s. Another approach might be to make some educated assumptions on the number of silent M.I.s in the cohort, the degree of imbalance possible between the aspirin and placebo groups, and provide an worst case analysis to show the result is still valid to show that aspirin prevents first heart attack. Although we doubt that there is much of an analgesic effect from 325 Q.O.D. of aspirin, you might see if there is data available on the analgesic dose response of aspirin. Perhaps you've discussed these matters before in your published reports, but I do not recall such considerations.

I hope you will evaluate these reports, and provide responses to the questions raised. We would be glad to discuss these reviews with you, and we look forward to your reply.

Sincerely yours,

Stephen Fredd, M.D.
Director
Division of Gastrointestinal
and Coagulation Drug Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research

cc:
IND 17,275
HFD-180
HFD-100/RTemple
HFD-110/RLipicky
HFD-100/ETriantas
HFD-180/SFredd
f/t deg: 9/11/89 SF 9/11/89
w0964b

BRIGHAM AND WOMEN'S HOSPITAL

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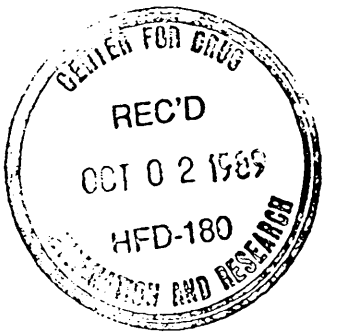
Department of Medicine
Channing Laboratory

September 28, 1989



Stephen Fredd, M.D.
Director
Division of Gastrointestinal and
Coagulation Drug Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research
Food and Drug Administration
Rockville, MD 20857

Dear Dr. Fredd:

Thank you for forwarding the Food and Drug Administration's medical and statistical review of the aspirin component of the Physicians' Health Study.

Attached is material that constitutes our reply to the review. Dr. James Taylor, as Chairman of the Endpoints Committee, provided me with the detailed response from the committee to the comments of the medical reviewer (Response to the Medical Review). This response includes an appendix addressing specific cases raised by the medical reviewer. Drs. Bernard Rosner and Nancy Cook, as the study statisticians, have provided me with the comments concerning the statistical review (Response to the Statistical Review).

We have also included, as attachments, copies of the following articles:

Attachment A: The final report from the aspirin component, which was published in the July 20, 1989 issue of the New England Journal of Medicine;

Attachment B: Galley proofs of an article entitled, "Aspirin and Other Antiplatelet Agents in the Secondary and Primary Prevention of Cardiovascular Disease," which will be published in the November, 1989 issue of Circulation;

Attachment C: The section on "Aspirin Prophylaxis" from the prepublication copy of the US Preventive Services Task Force report titled, Guide to Clinical Preventive Services, which has been submitted to Secretary of Health and Human Services Dr. Louis Sullivan; and

Attachment D: A draft copy of a manuscript currently being prepared on the clinical characteristics of nonfatal myocardial infarction in the Physicians' Health Study.

While interpretation of the meaning and significance of the aspirin findings of the Physicians' Health Study is the appropriate subject of debate and careful consideration, as are the choices and judgements made by the investigators in designing the trial, we are encouraged that the conduct of the trial according to the predefined methods and procedures, and the basic findings of the trial as reported, stand confirmed by the careful audit of the FDA reviewers.

Yours sincerely,

Charles H. Hennekens, M.D.

Enclosures

Orig N (YY)

BRIGHAM AND WOMEN'S HOSPITAL

Harvard Medical School

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Brookline, Massachusetts 02146
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Department of Medicine
Channing Laboratory

October 16, 1989

Ind 17-275

Steven Fredd, MD
Director
Division of Gastrointestinal and
Coagulative Drug Products
Food and Drug Administration
5600 Fishers Lane
HSD 180, Room 1092
Rockville, MD 20857

Dear Dr. Fredd: Steve

I am writing in follow-up to your telephone conversation today with Julie Buring. As reported in "Final Report on the Aspirin Component of the Ongoing Physicians' Health Study", 14.23% of the placebo group and 85.71% of the aspirin group reported use of either aspirin or any other platelet-active drugs. Since all analyses were performed on an intention to treat basis, this results in the reported relative risks for MI being underestimates of the true effect we would have observed with 100% compliance.

In terms of data on use of calcium channel blockers, beta blockers and other similar drugs, both prerandomization questionnaires asked about regular use (at least once per week) of any medications other than aspirin or vitamins. These data were coded according to the attached code list and entered into the computer. Since randomization, we have not explicitly collected information on the level of use of these medications. The presence of health conditions for which such medications might be prescribed would be indicators which we have on the level of their use postrandomization.

I hope this information answers your questions.

Kindest personal regards.

Yours sincerely,

Charles H. Hennekens

Enclosure

10/31/89

/ac
coct\fredd

cc: J. Buring
F. Stubblefield

BRIGHAM AND WOMEN'S HOSPITAL

Harvard Medical School

Charles H. Hennekens, MD, DrPH
Eugene Braunwald Professor of Medicine
Harvard Medical School
Chief, Division of Preventive Medicine
Brigham and Women's Hospital
900 Commonwealth Avenue East
Boston, MA 02215-1204

(617) 732-4965
(617) 731-3843 (Fax)

August 21, 1998

Dr. Debra L. Bowen
Acting Director
Division of OTC Drug Products
HFD 560
9201 Corporate Blvd.
Rockville, MD 20850

Dear Dr. Bowen:

As Principal Investigator of the Physicians' Health Study, I have no objections to the material included in our IND #17-275 being put on public display.

Sincerely,

Charles H. Hennekens

/ac
bowen.ind17275

cc: Ida Yoder

AUG 21 1998